IES
האגודה הישראלית לאנדוקרינולוגיה
Israel Endocrine Society

Affiliated with
European Society
of Endocrinology

הכנס המדעי ה-54

האגודה הישראלית לאנדוקרינולוגיה

15-16.7.2026

מלון דיוויד אינטרקונטיננטל | תל אביב

PROGRAM BOOKLET

שלום חברות וחברים,

ברוכים הבאים לכנס המדעי ה- 54 של האגודה הישראלית לאנדוקרינולוגיה.
השנה הוגשו לכנס למעלה מ- 170 תקצירים, המשקפים את המצוינות ורוחב היריעה
של המחקר האנדוקרינולוגי כפי שהוא מתבצע בבתי החולים,
באוניברסיטאות ומכוני המחקר ברחבי הארץ.

אנו מבקשים להודות למרצים האורחים שהגיעו לכנס ולישראל בזמנים אלו.
אנו מעריכים זאת מאוד!
וכמובן תודה רבה לכל המרצים, ליושבי הראש של המושבים,
ולבודקי התקצירים, על תרומתם להצלחת הכנס.

שנזכה לימים של שקט.
מאחלים לכולנו כנס מוצלח, פורה ומעשיר

פרופ' מרב פרנקל
נשיאת האגודה

פרופ' עמית עקירוב
מזכיר האגודה

פרופ' דני בן צבי
יו"ר שותף - כנס האביב

ד"ר אורית טויטו
יו"ר שותפה - כנס האביב

Platinum Sponsors:

ABBOTT

MEDISON

novo nordisk®

sanofi

Gold Sponsors:

Lilly
A MEDICINE COMPANY

REGENERON

Silver Sponsors:

AstraZeneca

NEOPHARM ISRAEL
NEOPHARM GROUP

Exhibitors:

astellas

BIOGENY
ThyroSeq
MOLECULARTESTING

Boehringer Ingelheim

CTS
Since 1921

medomie

minimed

NOVARTIS

Rafa.

SANDOZ

teva

Tzamal
BIO-PHARMA

פרופ' הנס יוחנן לינדנר ז"ל – מילים לזכרו

פרופ' הנס יוחנן לינדנר נולד בשנת 1922 בגרמניה ועלה ארצה עם הוריו בשנת 1936. לאחר מלחמת השחרור הוא למד רפואה וטרינארית בסידני (אוסטרליה) וסיים בהצטיינות.

את לימודיו לתואר לתואר Ph.D. הוא השלים באוניברסיטת קיימבריג' שבאנגליה. עם תום לימודיו, חזר לינדנר לאוסטרליה, התמנה כחוקר בכיר ב– Commonwealth Scientific Research Organization (CSIRO) והתרכז בחקר פיטואסטרוגנים. בשנת 1964, הגיע ארצה למכון ויצמן כחוקר אורח במח' לביודינמיקה.

כעבור שנה הוא קודם לדרגת פרופ' חבר ובשנת 1967 הוא מונה לראשות המחלקה.
פרופ' לינדנר בנה מחלקה מולטידיסיפלינארית שעסקה בחקרה פוריות ושינה את שמה ל: "חקר הורמונים."

בזכות תכונותיו התרומיות כאינטלקטואל וכמדען, נשא פרופ' לינדנר תפקידים רבים נוספים: הוא מונה במכון ויצמן כדיקן הפקולטה לביולוגיה, לראשות הועדה לקידום מדענים ולוועדה המייעצת של נשיא המכון. בנוסף לכך, הוא היה חבר בחבר הנאמנים של ביה"ח הדסה בירושלים, היה פעיל בהקמת הפקולטה לווטרינריה ואף היה נשיא האגודה הישראלית לאנדוקרינולוגיה.

בתקופת כהונתו החלה מסורת קיום הכנסים השנתיים. פרופ' לינדר היה פעיל גם בארגונים בינל"א: חבר בועדות WHO של מכון מקס פלאנק בגרמניה, של INSERN בצרפת, של ארגונים אנדוקריניים בינל"א וב– Editional Board של עיתונים מדעיים. הוענקו לו תארי כבוד במס' אוניברסיטאות בעולם.

בשנת 1979 הוענק לו פרס ישראל במדעי החיים והוא נבחר כחבר באקדמיה הישראלית למדעים.
בשנת 1982 הוענקו לו פרס רוטשילד בביולוגיה וכמו כן, פרס Axel–Munthe בשטח הביולוגיה של הפוריות.

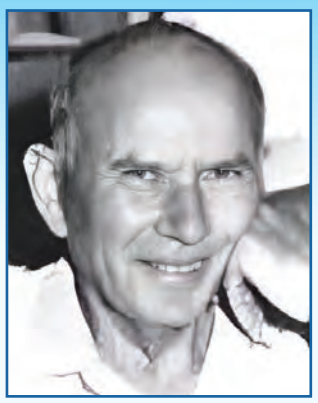
פרופ' הנס יוחנן לינדנר נפטר בשנת 1982 עקב מחלה קשה. כראש המחלקה לחקר ההורמונים הכשיר פרופ' לינדנר דורות של חוקרים בתחום האנדוקרינולוגיה. הפרס ע"ש פרופ' לינדנר הוא הפרס היוקרתי ביותר של האגודה הישראלית לאנדוקרינולוגיה.

הפרס ניתן לחוקר/ת,מתחת לגיל 50 עבור הישגים מדעיים בתחום האנדוקרינולוגיה במהלך חמש השנים האחרונות.

זוכי פרס לינדנר:

1989 – ישראל חנוקוגלו
1990 – מרדכי ליסקוביץ
1991 – ראובן רייך
1992 – אבי קרסיק
1993 – רוני זגר
1994 – עירית גרנות
1995 – אורי פלס
1996 – דורית אהרוני
1997 – חנה קנטי
1998 – בנימין גלזר
1999 – מיכל נאמן
2000 – רינה מידן
2001 – חיים ורנר
2002 – משה פיליפ
2003 – שרה פרבר
2004 – פואד פארס
2006 – איתן גרוס
2007 – אילן שמעון
2008 – חגית אדלר–פינקלמן
2009 – אסף רודיך
2010 – גיל ליבוביץ
2011 – אלון חן
2012 – פיליפה מלמד
2013 – יובל דור
2014 – ערן הורנשטיין
2015 – איילת ארז
2016 – ערן אלינב
2017 – סימונה גלסברג
2018 – גד אשר
2019 – ד"ר אייל רובינשטוק
2020 – ד"ר לימור לנדסמן
2022 – פרופ' אמיר תירוש
2023 – פרופ' גלעד טויג
2024 – פרופ' יוסי תם
2025 – פרופ' עמית תירוש
2026– פרופ' עידו גולדשטיין
פרופ' דני בן צבי

פרופ' ישראל חוברס ז"ל – מילים לזכרו



פרופ' חוברס נולד בפולין ב– 1923 והגיע לארץ בגיל חצי שנה.
את חינוכו היסודי קיבל בביה"ס החקלאי ע"ש מאיר שפיה. הוא היה פעיל במשך תקופה ארוכה בשורות ההגנה, בהבאת יהודים ארצה ובצה"ל.
הוא התקבל ללימודי הרפואה בשוויץ, אך בינתיים פרצה מלחמת העצמאות והוא החליט להישאר בארץ ולהשתתף בה באופן פעיל, בעיקר בהגנת אזור ירושלים. עם גמר המלחמה, סיים את לימודי הרפואה באוניברסיטה העברית בירושלים.

פרופ' חוברס שירת כרופא בית במחלקת עצבים ולאחר מכן השלים את התמחותו כרופא פנימי במחלקה פנימית בהדסה. מתוך עבודתו ברפואה פנימית ובנוירולוגיה, החל פרופ' חוברס להתעניין באנדוקרינולוגיה ואף היה בין הראשונים שקיבל תואר רופא מומחה בשטח זה בארץ. הוא התעניין במיוחד בתחום הנוירו–אנדוקרינולוגיה שבו תרם רבות מבחינה עיונית ומחקרית.

בשנת 1962 יצא פרופ' חוברס מטעם NIH להשתלמות באוניברסיטת פנסילבניה, שם עבד בשיתוף עם פרופ' McCann שעבודתו הקנתה לו מעמד של חלוץ במחקר האנדוקריני בתחום הקשר בין ההיפותלמוס והורמוני יותרת המוח, ובעיקר בגילוי ובאפיון של הפקטור ההיפותלמי המזרז את הפרשת הגונדוטרופינים מיתרת המוח (מאוחר יותר, זיהוי סופי של פקטור זה כ– LHRH ע"י Shally הקנה לו פרס נובל). עם שובו ארצה המשיך פרופ' חוברס את עבודתו במח' פנימית בביה"ח הדסה והועלה לדרגת פרופסור.
במקביל לעבודתו כרופא, הוא הקים מעבדת מחקר לאנדוקרינולוגיה ניסויית במסגרת מחלקת עצבים.
פרופ' חוברס וקבוצתו עסקו בחקר מנגנונים עצביים ואנדוקריניים הקשורים בוויסות חום הגוף ובתפקיד מערכת העצבים המרכזית בוויסות הפעלת הורמוני הדחק. כמו כן, עסקה מעבדתו בחקר יחסי הגומלין בין ההיפותלמוס האינסולין ורמת הגלוקוז בדם. מחקריו של פרופ' חוברס הקנו לו שם בינלאומי בתחום הנוירו–אנדוקרינולוגיה. הוא הוזמן להציג את מחקריו בפני כנסים בינלאומיים ושהה כמדען אורח באוניברסיטאות ובמכוני מחקר מהחשובים בעולם.

לצד עיסוקו ברפואה, במחקר ובהוראה, מצא פרופ' חוברס זמן לתת שירותים רפואיים ללא תמורה לאוכלוסייה מעוטת יכולת בירושלים. ב–1975 מונה פרופ' חוברס כמנהל המח' האנדוקרינית ומכון המחקר ע"ש רוגוף בביה"ח בילינסון. עם זאת, אהבתו לירושלים ולביתו בבית–זית ושאיפתו לעסוק ברפואה פנימית, על כל היבטיה, הביאו אותו לקבל את הצעת ביה"ח "ביקור חולים" לנהל את המח' הפנימית. על אף הקשיים הרבים שבהם היה נתון ביה"ח, ובמיוחד המח' הפנימית, הצליח פרופ' חוברס, בזמן קצר יחסית, לארגן צוות רופאים ועובדים ולשנות כליל את פני המחלקה.

ביוזמתו עבר ביה"ח שינויים ניכרים לקראת הפיכתו לבית–חולים מודרני ואוניברסיטאי. במסגרת שיקום המחלקה, הקדיש פרופ' חוברס תשומת לב רבה לשטח האנדוקרינולוגיה ובמיוחד לנושא הסוכרת.
הוא הקים יחידת סוכרת עם ציוד מודרני וייחודי להדרכה, אבחון, טיפול ומחקר קליני. במקביל לעבודתו בביה"ח ביקור חולים, מונה פרופ' חוברס כמנהל השירות האנדוקריני של קופ"ח הכללית בירושלים.
במסגרת זו הוא ארגן וניהל את מרפאת הסוכרת של קופ"ח בפרוז'ינין אשר סיפקה את שירותיה לאלפי חולי סוכרת במחוז י–ם.

פרופ' חוברס הקים וחינך דור של רופאים וחוקרים העוסקים ברפואה פנימית, אנדוקרינולוגיה וסוכרת.
הוא הדגיש תמיד את חשיבות הגישה החמה לחולה ובמיוחד לחולה הבודד והקשה. פרופ' חוברס, שהיה מוותיקי האגודה הישראלית לאנדוקרינולוגיה, נפטר באופן פתאומי ב– 3.2.89, לאחר מותו, יסדה משפחתו פרס לזכרו לשם קידום המחקר האנדוקריני בישראל.
הפרס מוענק לחוקר צעיר, מתחת לגיל 54 עבור עבודה בתחום האנדוקרינולוגיה שפורסמה בשנה האחרונה (או עומדת להתפרסם).

זוכי פרס חוברס:

1992 – דניאל מלול
1993 – טלי נוה–מני
1994 – ליאורה שוקובסקי
1995 – איריס קרן–טל
1996 – קרן פז
1997 – פואד פארס
1998 – אסף רודיך
1999 – סיגל כורם
2000 – אפרת וורטהיימר
2001 – אלון חן
2002 – רינה המי
2003 – יעל קלמה
2004 – שלומי לזר
2006 – אמיר תירוש
2007 – נועה שר וערן גרשון
2008 – עירית מיבר–לוי
2009 – עידו וולף
2010 – מוריר חמאיסי
2011 – רעות אשואל
2012 – יעל קופרמן
2013 – יונית מרקוס
2014 – דנה חודרלנד
2015 – יעל שרגא–לוי
2016 – בני גורפינקל
2017 – עמית עקירוב
2018 – יוסי תם
2019 – ד"ר יעל ריאחי
2020 – ד"ר מיכל סילבר
2022 – ד"ר נעה גרובר
ד"ר דני בן צבי
2023 – ד"ר רנא הלון
ד"ר עידו גולדשטיין
2024 – ד"ר אביבית ברנר
2025 – פרופ' יותם דרייר
ד"ר יהושוע סטוקאר
2026 – ד"ר רגב לנדאו

פרופ' אורי אהרון ליברמן ז"ל – מילים לזכרו

פרופ' אורי אהרון ליברמן ז"ל, היה פורץ דרך בשדה האוסטיאופורוזיס בישראל ובעולם. רופא, חוקר ומורה דגול.

קצרה היריעה מלהציג את הישגיו ורשימת תפקידיו, שכללו, בין השאר, וועדות מדעיות בארץ ובעולם, פרסום אין ספור מאמרים בעיתונים מדעיים מובילים וכתיבת פרקים בספרי לימוד שזיכו אותו בפרסים ומענקי מחקר.

במרוצת השנים הכשיר במעבדתו עשרות רופאים וסטודנטים לדוקטורט ולתואר שני, הממשיכים את דרכו ותורמים לקידום המחקר והטיפול הרפואי.
פרופסור ליברמן הוביל מחקרים פורצי דרך, בין היתר מחקרי יעילות קלינית של Alendronate.

ב- 1998 יזם והקים את 'עילא' העמותה הישראלית לאוסטיאופורוזיס ומחלות עצם והיה יו"ר פעיל עד יום מותו. בנותיו, עו"ד מיכל ליברמן ופרופ' תמר ליברמן גולט, בחרו להנציח את שמו בהענקת פרס שנתי – ציון לשבח לרופא ו/או לחוקר בתחום האוסטיאופורוזיס, מטבוליזם ומינרלים של העצם בישראל, אשר הגיעו להישגים בתחומם בעת האחרונה.

זוכי פרס ליברמן:

2023 – ד"ר איריס ורד
2024 – פרופ' רבקה דרזנר-פולק
2025 – ד"ר רקפת בכרך
2026 – פרופ' יעל-לוי שרגא
ד"ר מיכל כשר-מירון (פרס המצוינות לחוקרים צעירים בתחום האוסטאופורוזיס, ומטבוליזם)

INVITED SPEAKERS

Prof. George J Kahaly

George J Kahaly, M.D., Ph.D. holds the rank of Professor of Medicine and Endocri-nology / Metabolism at the Johannes Gutenberg University (JGU) Medical Center, Mainz, Germany. As senior physician, Dr. Kahaly directs the endocrine autoimmunity outpatient clinic and chairs the referral expert ORPHAN center for Graves' orbitopathy & autoimmune polyendocrinopathy.
Dr. Kahaly directs the referral accredited & certified academic Thyroid Laboratory and has authored 424 original papers, reviews, book chapters and books covering clinical, experimental, and immune genetic aspects of endocrine autoimmunity, as well as car-diovascular involvement of metabolic disorders. Research articles and reviews have been published in the New England Journal of Medicine, Lancet, JAMA, Annals of Internal Medicine, the Journal of Clinical nvestigation, Nature Communications, Clini-cal Chemistry, the Journal of Autoimmunity, the Journal of Clinical Endocrinology and Metabolism, the Journal of Nuclear Medicine, Endocrinology, Thyroid, Endocrine Re-views, Nature Reviews and Autoimmunity Reviews (H-index 81, 26,404 citations).
Dr. Kahaly is the 2024 recipient of the European Thyroid Association (ETA) "Aldo Pinchera" Award. Further, he is the 2022 recipient of the "Jacques Genest" Award of the Canadian Society of Endocrinology & Metabolism. Dr. Kahaly also is the 2019 re-cipient of the American Association of Clinical Endocrinologists / American College of Endocrinology (AACE/ACE) International Endocrinology Award. He also is the 2019 recipient of the British Thyroid Association "George Murray Award". Dr. Kahaly has received several further awards: British Medical Association Book Award (2018); Best Reviewer Award, European Thyroid Journal (2018); Poster prize, German Endocrine Society (2006, 2008, and 2009); Poster prize, German Society of Internal Medicine (2006 & 2008), and Best Poster Prize, international thyroid eye disease congress, London 2025.
Dr. Kahaly is Editor of the textbook DeGroots' Endocrinology (8th & 9th Ed.). He served 2015-2019 as Editor of the Journal of Clinical Endocrinology & Metabolism, official or-gan of the American Endocrine Society. In the years 2009-2012, he was Associate Editor of the journal Thyroid, official journal of the American Thyroid Association (ATA). Dr. Kahaly is also member of the Editorial Board of the European Thyroid Journal, official journal of the European Thyroid Association (ETA). Further, he was member of the scientific program-organizing committees of the 2020 International Thyroid Con-gress, Xian, China as well as of the 2020 spring meeting of the ATA. Finally, Dr. Kahaly was member of the Publication Core Committee of the American Endocrine Society (2020-2023).
Dr. Kahaly served as Treasurer and principal officer of the Executive Committee of the ETA between 2007 and 2016. Since 2000, he has also served on numerous ATA Com-mittees (Laboratory Services Committee 2018-2022, Public Health 2015-2018, Re-search 2012-2015, Finance and Audit 2007-2011, as well as Membership and Publi-cation Committees 2000-2006). Further, Dr. Kahaly served for 17 consecutive years as Treasurer and principal officer of the Executive Committee of the European Group on Graves' Orbitopathy (EUGOGO) 2004-2021. In the years 2005-2011, he was mem-ber of the Executive Committee of the German Thyroid Board.

Prof. Martyn Caplin

Prof. Martyn Caplin is Professor of Gastroenterology & Neuroendocrine Cancer Biology at the Royal Free Hospital and University College London. He leads The Royal Free Hospital's "European Neuroendocrine Tumour Society Centre of Excellence". Furthermore, he leads scientific and clinical research programmes into neuroendocrine tumours across University Colle ge London. He has been chief investigator and principal investigator in many key clinical trials. He is a founder and a past chair of both UK and also European Neuorendocrine Tumor Societies. He received a lifetime achievement award for his leadership and research into these rare cancers. In the field of gastroenterology he was the clinical lead for "NHS Evidence" for Gastroenterology and Liver diseases (under the auspices of NICE), chairing annual evidence updates into gastrointestinal and liver disorders. He additionally has a special interest in diet and its impact on disease. He has published over 250 peer review papers, written multiple book chapters and co-authored two books. He regularly lectures both nationally and internationally.

Prof. Klaus H. Kaestner

Klaus H. Kaestner, Ph.D., M.S. is the Suor Butterworth Professor of Genetics at the University of Pennsylvania School of Medicine and Associate Director of Penn's Institute for Diabetes, Obesity and Metabolism as well as Penn's prestigious NIH-funded Diabetes Research Center. Since 2016, Dr. Kaestner has been Principal Investigator of the NIH-funded Human Pancreas Analysis Program for Type 1 Diabetes (T1D), which was selected as the sole US center to direct and coordinate the deep phenotyping of the human endocrine pancreas to better understand the cellular and molecular events that precede and lead to beta-cell loss and/or dysfunction in T1D. Because of the success of the program, and the world-wide usage of its unique datasets, the NIH has renewed and expanded it twice. Dr. Kaestner's work groundbreaking work is focused on the understanding of the molecular mechanisms of beta-cell mass expansion and glucose homeostasis. In addition, his laboratory has pioneered the development of functional genomics tools applicable to the study of the human endocrine pancreas. Dr. Kaestner has lectured around the world and has served as Associate Editor for Diabetes and the Journal of Clinical Investigation. He has received an NIH MERIT award in 2012, the Roy O. Greep Award for Outstanding Research, the Endocrine Society in 2017, and the Albert Renold Prize from the European Association for the Study of Diabetes in 2026 in recognition for his contribution to our understanding of the endocrine pancreas and T1D.

SCIENTIFIC PROGRAM

Wednesday, July 15, 2026

07:30–08:30 **Registration, Refreshments & Visit the Exhibition** Foyer

08:30–10:00 **Parallel Sessions – Oral Presentations from Selected Abstracts**

08:30–10:00 **Parallel Sessions – Abstracts** Hall A
Obesity
Chairs: Prof. Avivit Brener, Dr. Michal Kasher Meron

08:30–08:42 **Differentiating Mouse and Human Adipose Tissue Derived Fatty Acid Binding Protein 4 (FABP4) in the Regulation of Cancer Growth**
Nicole Geller[1,2], Rinat Livne[1], Reem Igbaria[1,2], Amir Tirosh[1,2]
[1]The Dalia and David Arabov Endocrinology and Diabetes Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv University

08:42–08:54 **Human Gastric Organoids as a Platform to Study Ghrelin Cell Differentiation and Function**
Amit Elad[1], Deborah Duran[2], Michelle Malis[1], Haya Benhayon[1], Dana Orzech[1], Esther Forkosh[3], Orli Halstuk[2], Doron Kleiman[1], Ariel Benson[3], Ronit Grinbaum[4], Idit Shiff[5], Abed Nasereddin[5], Liron Birimberg-Schwartz[2], Rachel Ben-Haroush Schyr[1], Myriam Grunewald[2], Danny Ben-Zvi[1]
[1]Department of Developmental Biology and Cancer Research, The Hebrew University of Jerusalem, [2]Organoid Center, Hadassah University Medical Center, [3]Institute of Gastroenterology and Liver Disease, Hadassah University Medical Center, [4]Department of Surgery, Hadassah-Hebrew University Medical Center, [5]Genomics Applications Laboratory, Core Research Facility, The Hebrew University of Jerusalem

08:54–09:06 **Adolescent to Adulthood Weight Trajectories and the Risk of Cancers**
Gilad Twig[5], Cole Bendor[1], Aya Bardugo[1], Avishai Tsur[1], Estela Derazne[2], Itay Shemesh[3], Lotmit Bourvine, Dror Dicker[4], Ben Boursi[5], Amir Tirosh[5], Arnon Afek[5], Ran Rotem[6], Gabriel Chodick[2]
[1]Israel Defense Forces, [2]Tel-Aviv University, [3]Novo Nordisk, [4]Rabin Medical Center, [5]Sheba Medical Center, [6]T.C. Chan School of Public Health, Harvard University, MA, USA

09:06–09:18 **Fib-4 Index Predicts Chronic Kidney Disease**

Viviana Ostrovsky[1], Hilla Knobler[2], Arad Dotan[3], Saghi Tshori[4], Shay Ben-Haim[5], Taiba Zornitzki[1]

[1]Hebrew University of Jerusalem, the Faculty of Medicine, Israel, Diabetes, Endocrinology and Metabolic Disease Institute, Kaplan Medical Center, Rehovot, Israel, [2]Hebrew University of Jerusalem, the Faculty of Medicine, Israel, Diabetes Institute, Meuhedet HMO, Israel, [3]The Faculty of Medicine, Tel Aviv University, Israel, Sheba Medical Center, Ramat Gan, Isreal [4]Hebrew University of Jerusalem, the Faculty of Medicine, Israel, Heart Institute, Kaplan Medical Center, Rehovot, Israel, [5]Hebrew University of Jerusalem, the Faculty of Medicine, Israel, Braun School of Public Health and Community Medicine. The Hebrew University and Hadassah Medical Center

09:18–09:30 **The Effects of 10 Weeks of Time-Restricted Eating, Resistance Training, and Their Combination on Body Fat Depots and Low-Grade Inflammation in Patients with Metabolic Syndrome**

Roi Yavetz[1,2], Ron Sternfeld[1,2], Yair Lahav[1,2], Michal Rein[3], Shira Zelber Sagi[3], Hasan Ishtayeh Ishtayeh[4], Avraham Ashkenazi[4], Nir Polak[5], Shai Efrati[5], Yftach Gepner[6,7]

[1]Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Gepner Lab, [2]Tel Aviv University, Sylvan Adams Sport Institute, [3]University of Haifa, School of Public Health 4Tel Aviv University, Sagol School of Neuroscience, [5]Shamir Medical Center (Assaf Harofeh), Sagol Center for Hyperbaric Medicine and Research 6Department of Epidemiology and Prevention Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Gepner Lab, [7]Tel Aviv University, Sylvan Adams Sport Science Institute

09:30–09:42 **Adolescent Body Mass Index and Multimorbidity Before Age 50**

Avishai M. Tsur[1,2], Estela Derazne[1,3], Arnon Afek[4], Gabriel Chodick[3], Gilad Twig[5,6]

[1]Medical Corps, Israel Defense Forces, [2]Faculty of Medicine, Department of Military Medicine, Hebrew University of Jerusalem, [3]Faculty of Medical and Health Sciences, School of Public Health, Tel Aviv University, [4]Dina Recanati School of Medicine, Reichman University, [5]The Institute of Endocrinology Diabetes and Metabolism, Sheba Medical Center, [6]Department of Preventive Medicine and Epidemiology, School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University

09:42–09:54 **A Clinical Scoring System to Guide Genetic Evaluation in Pediatric Obesity**

Hanna Ludar[1], Shira London[1,2], Inbal Halabi[1,3], Keren Cohen[1], Majdoub Hussein[1], Ghadir Elias-Assad[4,5], Ilana Koren[1]

[1]Pediatric Endocrine and Diabetes clinic, Clalit Health Services, Haifa and west Galili District, Israel, [2]Pediatric Endocrine and Diabetes Unit, Rambam medical center, [3]Pediatrics unit, Carmel medical center, [4]Pediatric Endocrine Clinic, Clalit Health Services, Northern region, Israel, [5]Pediatric Endocrine Institute, Saint Vincent Hospital, Nazareth, Israel

08:30–10:00 Parallel Sessions – Abstracts — Hall B

Adrenal and Fertility

Chairs: Dr. Gabriel Munter, Dr. Amir Bashkin

08:30–08:42 **The GAPP Aggressivity Score Correlates with Somatic Non-Missense Mutation Burden in Pheochromocytoma**

Reut Halperin[1,2], Gil Goldinger[3], Eddie Fridman[3], Naama Peshes Yaloz[1], Amit Tirsoh[1,2], Gadi Shlomai[2,4]

[1]ENTIRE – Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba MC, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv University, [3]Pathology, Sheba MC, [4]Division of Endocrinology, Diabetes and Metabolism, Sheba MC

08:42–08:54 **Association between Somatic Mutations in Cortisol-Secreting Adrenal Adenomas and Clinical-Demographic Features: A Single-Center Study of 112 Cases**

Hadas Rabani[1], Nina Nazarov[2], Hila Shefer[2], Mohammad Sheikh-Ahmad[1,3], Anan Shalata[1], Katya Jovanovic[1], Jacob Bejar[2], Leonard Saiegh[1,3]

[1]Endocrinology department, Bnai Zion Medical Center, [2]Pathology department, Bnai Zion Medical Center, [3]The Ruth and Bruce Rappaport Faculty of Medicine, Technion

08:54–09:06 **New-Onset Autoimmune Endocrine Disorders in People Living with Post-Traumatic Stress Disorder**

Yovel Cohen[1,2], Meir Schechter[1,2], Dvora Rywka Sehtman-Shachar[1,2], Ofri Mosenzon[1,2,3], Genya Aharon-Hananel[1,2], Gil Leibowitz[1,2]

[1]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center of the Hebrew University, Jerusalem, Israel, [2]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, [3]Regeneron Pharmaceuticals Inc., New York, New York, USA

09:06–09:18 **Real-World Multicenter Outcomes following Transition to Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia and Adrenal Insufficiency**

Anat Segev-Becker[1], Talia Jacobi-Polishook[2], Liat Perl[1], Larisa Nauogolny[3], Jessica Sack[4], Nitzan Dror[5], Alon Eliakim[5], Shirli Abiri[6], Tal Ben Ari[6], Rivka Dresner-Pollak[7], Yael Levy-Shraga[8], Meir Frankel[9], Neta Loewenthal[10], Michal Cohen[11], Merav Fraenkel[12], Dmitry Shklovski[13], Nir Lasman[14], Alina German[15], Yardena Tenenbaum Rakover[16], Dania Hirsch[17], Svetlana Turkot[18], Mzia Sapir[19], Liza Paley[18], Liat Sasson[17], Marianna Rachmiel[2], Miriam Steinschneider[20], David Shaki[21], Sigal Shaklai[4], Ilana Zalmon Koren[22], Naomi Weintrob[23]

[1]The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Pediatric Endocrinology Institute, Shamir (Assaf Harofeh) Medical Center, Beer Yaakov, Israel. 3Meuchedet Health Services, Rishon LeZion, Israel, [4]Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, [5]Pediatric Endocrinology Unit, Meir Medical Center, Kfar-Saba, Israel, [6]Pediatric Endocrinology and Diabetes Unit, Edith Wolfson Medical Center, Holon, Israel, [7]Department of Endocrinology, Hadassah Medical Center, Jerusalem, Israel, [8]Pediatric Endocrine and Diabetes Unit, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel, [9]Endocrinology Unit, Shaare Zedek Medical Center, Jerusalem, Israel [10]Pediatric Endocrinology Unit, Ben Gurion University Medical Center, Beer Sheva, Israel, [11]Pediatric Endocrinology Unit, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel, [12]Endocrine Unit, Soroka Medical Center, Beer-Sheva, Israel, [13]Endocrinology, Clalit Health Service South District, [14]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel-Hashomer, Israel, [15]Pediatric Endocrinology and Diabetes Unit, HaEmek Medical Center, Afula, Israel [16]Children's Endocrinology Consulting Center, Clalit Health Services, Afula, Israel, [17]Institute of Endocrinology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel, [18]Barzilai medical center, [19]Clalit Migdal Hamea, Tel Aviv, [20]Endocrine and diabetes institute, Shamir (Assaf Harofeh) Medical Center, Beer Yaakov, Israel, [21]Pediatric Endocrinology Unit, Soroka University Medical Center, Beer Sheva, Israel, [22]Pediatric Endocrinology Unit, Lady Davis Carmel Medical Center and Clalit Health Services, Haifa, Israel, [23]Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

09:18–09:30 **Nutraceutical Rescue of Methylprednisolone-Induced Myotube Atrophy: Evidence from C2C12 Morphometry**

Gilad Lehmann[1], Yona Greenman[1], Yonit Marcus[1], Miguel Morales Moshiashvili[1], Gabi Shefer[1]
Endocrinology, Tel-Aviv Sourasky Medical Center (Ichilov)

09:30–09:42 **A Role for Foxl2 in Maintaining Open Chromatin at a Lineage-Specific Distal Regulatory Element of the Fshb Gene**

Daniella Darsa[1], Gil Golan[1], Tal Refael[1], Lilach Pnueli[1], Philippa Melamed[1]
Faculty of Biology, Technion-Israel Institute of Technology

09:42–09:54 **Long-Term Health Issues Related to Differences in Sex Development**

Liat de Vries[1,2], Orit Futterman[1,2], Amit Eben Chaime[1,2], Moshe Phillip[1,2], David Ben Meir[2,3]
[1]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, [2]Faculty of Medical & Health Sciences, Tel Aviv University
[3]Pediatric Urology Unit, Schneider Children's Medical Center of Israel

08:30–10:00 **Parallel Sessions – Abstracts** Hall D

Bone

Chairs: Dr. Rachel Rosenblum, Dr. Irit Wirzansky Pearl

08:30–08:42 **An AI-Assisted Tool for Automated Growth Monitoring in Pediatric Achondroplasia**

Eyal Cohen-Sela[1,2], Yael Lebenthal[1,2], Avivit Brener[1,2], Ravit Regev[1,2], Lars Hagenäs[3]
[1]The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]The School of Medicine, Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel [3]Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden

08:42–08:54 **Body Mass Index and Incidence Stress Fractures in a Nationwide Cohort of 193,047 Young Women and Men in Combat Training**

Adi Horesh[1,2], Bar Weinstein[3], **Romi Halperson**[1,2], Omer Itzkovitch[1], Shlomi Abuhasira[1,2], Ziv Talmi[1,2], Ron Skorochord[1,2], Yitzchak Elefant[1,2], Yigal Chechik[1,4], Doron Yaya-Stupp[1,2], Aya Bardugo[1,2], Itay Ketko[1,2], Meir Schechter[1,5]

[1]Medical Data Research Institute, Israel Defense Forces Medical Corps, Tel HaShomer, Ramat Gan, Israel, [2]Institute for Research in Military Medicine, Faculty of Medicine, Hebrew University of Jerusalem, Israel, [3]School of Mathematical Sciences, Tel Aviv University, Tel Aviv, Israel, [4]Department of Orthopedics, Shamir Medical Center, Be'er Yacob, Israel, [5]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel

08:54–09:06 **GLP-1-Receptor Agonists Directly Reduce Proliferation in ATDC5 Chondrocytes**

Irit Meivar Levy[1,2], Biana Shtaif[1,3], Galia Gat-Yablonski[1,3], Moshe Phillip[1,3], Naama Fisch-Shvalb[1,3]

[1]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center, [2]Felsenstein Medical Research Center, [3]Gray Faculty of Medical and Health Sciences, Tel Aviv University

09:06–09:18 **Real-world Safety of Romosozumab in High Cardiovascular Risk Patients**

Joshua Stokar[1,2], Auryan Szalat[1,2]

[1]Departments of Medicine & Endocrinology, Hadassah Medical Center

[2]Faculty of Medicine, The Hebrew University of Jerusalem

09:18–09:30 **Sustained Hyperglycemia Induces Senescence in Osteocyte-Like Cells**

Natan Lishinsky-Fischer[1], Irina Gurt[2], Vladislav Temkin[2], Joshua Stokar[1,2], Rivka Dresner-Pollak[1,2]

[1]The Faculty of Medicine Hebrew University of Jerusalem, Israel, [2]Department of Endocrinology and Metabolism, Division of Medicine, Hadassah Medical Organization, Jerusalem, Israel

09:30–09:42 **Family History Predicts Primary Hyperparathyroidism Regardless of Genetic Predisposition**

Reut Halperin[1,2], Liana Tripto-Shkolnik[2,3], Iris Vered[3], Pinchas Klein[2,3], Galit Avior[2,4], Hadar Miloh-Raz[2,3], Jacob Ilani[3], Naama Peltz-Sinvani[2,3], Tali Cukierman-Yaffe[2,3], Nir Lasman[2,3], Sigal Ben-Shmuel[3], Amna Jabarin[2,3], Yehudit Eden-Friedman[2,3], Gil Goldinger[2,5], Gadi Shlomai[2,3], Naama Pashes-Yaloz[1,2], Amit Tirosh[1,2]

[1]ENTIRE – Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba MC, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv University, [3]Division of Endocrinology, Diabetes and Metabolism, Sheba MC, [4]Department of Otolaryngology-Head and Neck Surgery, Sheba MC, [5]Pathology, Sheba MC

09:42–09:54 **High and Very High-Risk Fracture Risk Among Patients with a Non-Osteoporotic Range Bone Mineral Density in a DXA Database from a Tertiary Medical Center**

Yehudit Eden-Friedman[1,2], Iris Vered[1], Nimrod Tripto[3], Noga Minsky[1,2], Pnina Rotman-Pikielny[2,5], Yael Levy-Shraga[2,4], Liana Tripto-Shkolnik[1,2]

[1]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, [3]Recah Institute of physics, The Hebrew University of Jerusalem, Jerusalem, Israel, [4]Pediatric Endocrinology Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center 5Department of Endocrinology, Meir Medical Center

08:30–10:00 **Parallel Sessions – Abstracts** Hall H

Type 1 Diabetes

Chairs: Dr. Aharon Helman, Dr. Noga Minsky

08:30–08:42 **δ-Cell Inhibition Renews β-Cells and Insulin Independence in Diabetes**

Ron Piran[1], Yara Hamshawi[1], Nagham Gudban[1], Florin-Daniel Bîlbîe[2], Daljeet Kaur[1], Manar Hijazi[1], Yael Riahi[3], Offir Ertracht[4], Maria Naama[1], Rita Bottino[5], Assaf Malka[1], Shai Bel[1], Shaul Atar[4], Gil Leibowitz[3], Andrei Păun[6,7]

[1]The Azrieli Faculty of Medicine, Bar-Ilan University, [2]National Institute of Research and Development for Biological Sciences, [3]Faculty of Medicine, Hebrew University of Jerusalem, [4]Galilee Medical Center, Eliachar Research Laboratory, [5]Imagine Pharma, [6]ICUB/Faculty of Mathematics and Computer Science, University of Bucharest, [7]Research Institute for Artificial Intelligence, Romanian Academy

08:42–08:54 **A Temporal Map of Autoimmune Diabetes Progression Based on RNA Sequencing of Single Islets Reveals Distinct Patterns of Islet Deterioration**

Tsofiya Szanton[1], Nadav Sharon[1], Paraskevas Filippidis[2], Gur Yaari[2]
[1]Faculty of Biology, Technion, [2]Department of Pathology, Yale School of Medicine

08:54–09:06 **Immune Activation and α–Cell Identity Remodeling Define Transcriptional States in Type 1 Diabetes**

Haya Benhayon[1,2], Michael M Danziger[3], Danny Ben–Zvi[1,2], Michal Rosen–Zvi[2,3]
[1]Institute of Medical Research Israel–Canada, the Hebrew University–Hadassah Medical School, Developmental Biology and Cancer Research, [2]The Hebrew University, Faculty of Medicine, [3]IBM Research – Israel

09:06–09:18 **Impact of Autoimmune Hypothyroidism and Celiac Disease on Progression to Diabetes in GAD– or IA–2 Positive Individuals**

Afif Nakhleh[1,2], Naim Shehadeh[1,2]
[1]Maccabi Healthcare Services, Haifa, Israel, [2]The Azrieli Faculty of Medicine, Bar–Ilan University, Safed, Israel

09:18–09:30 **The Impact of Meal Bolus Timing and Rescue Strategies with Advanced Hybrid Closed–Loop Systems**

Maya Laron Hirsh[1], Noga Minsky[1], Andrea Benedetti[2], Roy Anirban[2], Benyamin Grossman[2], Ohad Cohen[2], Amir Tirosh[3]
[1]Endocrinology, Diabetes and Metabolism, Sheba Medical Center, [2]Medtronic, [3]Endocrinology, Sheba Medical Center

09:30–09:42 **HLA Genotype, BMI Status, and Young–Adult–Onset Type 1 Diabetes**

Gilad Twig[2], Cole Bendor[1], Aya Bardugo[1], Amir Tirosh[2], Sapir Israeli[3], Estela Derazne[4], Inbar Zucker[5], Miri Lutski[5], Ariel Furer[1], Zivan Aviad–Beer[1], Orit Pinhas–Hamiel[2], Gabriel Chodick[4], Bracha Zisser[6], Arnon Afek[2], Hertzel Gerstein[7], Tali Cukierman–Yaffe[2], Sigal Manor[6], Yoram Louzoun[3]
[1]Israel Defense Forces, [2]Sheba Medical Center, [3]Bar–Ilan University, [4]Tel–Aviv University, [5]Israel Ministry of Health, [6]Ezer Mizion Bone Marrow Donor Registry, [7]McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

09:42–09:54 **Effect of Hyperbaric Oxygen Therapy in Youth with Newly Diagnosed Type 1 Diabetes: A Randomized Controlled Proof-of-Concept Trial**

Avigail Wittenberg[1,2], Dana Arad[1,3], Sharon Shtrausman[4], Orit Pinhas-Hamiel[5,6], Shai Efrati[6,7], **Marianna Rachmiel**[1,6]

[1]Pediatric Endocrinology and Diabetes Institute, Shamir (Assaf Haroffeh) Medical Center, [2]Department of Pediatrics, Division of Endocrinology, University of British Columbia, Vancouver, BC, Canada, [3]Koret school of Veterinary Medicine, Hebrew University of Jerusalem, [4]Pediatric Endocrine Unit, Kaplan Medical Center, Rehovot, Israel, [5]Pediatric Endocrine and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Ramat-Gan, Israel, [6]Gray School of Medicine, Tel Aviv University , Tel Aviv, Israel, [7]Sagol Center for Hyperbaric Medicine and Research, Shamir Medical Center

10:00–10:30 **Coffee Break & Visit at the Exhibition** Foyer

10:30–10:50 **Opening Session** Hall B

Greetings and Association Updates

Prof. Merav Fraenkel | President, Israel Endocrine Society, Head of Endocrine Service, Soroka University Medical Center, Faculty of Health Science, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Dr. Orit Twito | Head of Endocrinology and Diabetes Unit, Wolfson Medical Center, Holon

Prof. Danny Ben-Zvi | Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem

Prof. Amit Akirov | Endocrine Institute, Rabin Medical Center, Petah-Tikva; Secretary of the Israel Endocrine Society

10:50–11:35 **Plenary 1** Hall B

Chair: **Prof. Amit Akirov**

10:50–11:35 **The Journey of Somatostatin Analogues in Acromegaly Treatment**

Prof. Ilan Shimon | Institute of Endocrinology, Rabin-Beilinson Medical Center, and Gray Faculty of Medicine, Tel-Aviv University

11:45–12:35	**Parallel Session 1– Gestational Diabetes** Chair: **Dr. Yoel Toledano**	Hall A
11:45–12:10	**Panel: Personalizing Diabetes Care in Pregnancy: Evidence, Controversies and Clinical Decision–Making** Moderator: **Dr. Yoel Toledano** | Rabin Medical Center, Petah–Tikva **Dr. Tamar Eshkoli** | Obstetric Endocrinology Coordinator, Department of Obstetrics and Gynecology, Endocrinology Unit, Soroka University Medical Center, Beer–Sheva **Dr. Orit Barenholz–Goultschin** | Head of MFM unit, Laniado, District diabetes physician Meuhedet, Jerusalem **Dr. Tal Schiller** | Lead of the Diabetes and Obesity field, Endocrinology Unit, Wolfson Medical Center, Holon	
12:10–12:35	**GDM and the Postpartum Care Gap** **Dr. Tal Schiller** | Lead of the Diabetes and Obesity field, Endocrinology Unit, Wolfson Medical Center, Holon	
11:45–12:35	**Parallel Sessions 1 – Fertility Basic** Chair: **Prof. Nitzan Gonen**	Hall B
11:45–12:10	**Functional Heterogeneity in Circadian Control of the Female Estrous Cycle** **Dr. Anat Kahan** | Animal Sciences Department, The Faculty of Agriculture, The Hebrew University, Rehovot	
12:10–12:35	**The Impact of Stress on Fertility and Beyond** **Dr. Eran Gershon** | Department of Ruminant Science, Animal Science Institute, ARO, Rishon LeZion	
11:45–12:35	**Parallel Sessions 1 – Bone Metabolism** Chairs: **Dr. Vanessa Rouach**, **Dr. Auryan Szalat**	Hall D
11:45–12:10	**How Do We Untie the Triangle? A Triangular Dialogue Between Two Dentists and an Endocrinologist** **Prof. Pnina Rotman–Pikielny** | Institute of Endocrinology, Diabetes and Metabolic Bone Diseases **Dr. Ronit Cagan** | Oral and Maxillofacial Surgeon **Dr. Victoria Yaffe Gartsbein** | Oral and Maxillofacial Surgeon	
12:10–12:35	**The DXA you didn't Order: Osteoporosis Detection Through Opportunistic Imaging** **Dr. Yehudit Eden–Friedman** | Institute of Endocrinology, Sheba Medical Center, Tel–Hashomer	

12:45–13:30	**Satellite Lunch's & visit at the Exhibition**	
12:45–13:30	**Satellite Lunch – Beyond Limits: Biologic Breakthroughs in Bone and Thyroid Eye Disease Care** Sponsored by: **Medison**	**Hall H**
12:45–13:00	**BMD is Back in Business?** **Dr. Liana Tripto–Shkolnik** | Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center	
13:00–13:15	**Phosphaturic Mesenchymal Tumors: Contemporary Insights from a Tertiary Referral Center** **Dr. Liana Tripto–Shkolnik** | Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center	
13:15–13:30	**Living with Thyroid Eye Disease: A Patient and Physician Dialogue** LIORT, The Israeli Research Association for Eye Health and Blindness Prevention (R.A)	
12:45–13:30	**Satellite Lunch – GLP–1 Signaling Beyond the Receptor: Intracellular Mechanism and Clinical Meaning** Sponsored by: **NovoNordisk**	**Hall I**
12:45–12:55	**GLP 1: Ligand, Receptor, and Intracellular Signaling** **Prof. Amir Tirosh** | Director of the Institute of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel HaShomer	
12:55–13:05	**Integrating Mechanistic Understanding with Clinical Data** **Prof. Avivit Cahn** | Head of Internal Medicine Department A, Hadassah Ein Kerem; Chair, National Council for Diabetes and Obesity ;Chair, Israeli Society for Diabetic Foot and Wound Healing	
13:05–13:15	**Mechanistic Aspects of CV Benefit Independent of Weight Loss: Insights from SELECT** **Dr. Idit Dotan** | Head of the Diabetes Unit, Head of the Multi–Disciplinary center for the Treatment of Obesity, The Division of Endocrinology, Diabetes and Metabolic Diseases, Rabin Medical Center, Beilinson Campus	
13:15–13:30	**Panel discussion: Implementing Science in Clinical Practice**	
12:45–13:30	**Satellite Lunch – Emerging Therapies in Sarcopenia: Bridging Muscle Preservation and Functional Recovery** Sponsored by: **Regeneron**	**Hall J**

12:45–13:00	**Nutrition for Muscle Preservation** Hagar Shimon | Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center; Maccabi Health Care Services, Diabetes clinic, Netanya	
13:00–13:15	**Exercise and Resistance Training for Prevention & Treatment of Sarcopenia** Dr. Tal Yahalom-Peri | Epidemiology Department, School of Public Health, Gray Faculty of Medical & Health Sciences, Tel Aviv University; Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center	
13:15–13:30	**Pharmacological Agents for Prevention & Treatment of Sarcopenia** Prof. Ofri Mosenzon | Executive Medical Director, Regeneron Pharmaceuticals, Tarrytown, NY, USA	
13:30–14:10	**Posters Exhibition & Lunch**	Foyer
14:10–14:55	**Plenary Session** Chair: Prof. Taiba Zornitzky	Hall B
14:10–14:55	**Studying Diabetes via the Human Pancreas Analysis Program (HPAP): What have we Learned?** Prof. Klaus Kaestner | School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	
15:00–15:50	**Parallel Session 2 – Thyroid** Chairs: Prof. Eyal Robenshtok, Dr. Sagit Zolotov	Hall A
15:00–15:25	**Clinical Dilemmas in Thyroid Disease: What's New in the Past Year** Dr. Keren Kaminer| Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center, Beilinson Campus, Petah Tikva	
15:25–15:50	**Graves Disease** Prof. George J. Kahaly | Professor of Medicine and Endocrinology/ Metabolism Johannes Gutenberg University (JGU) Medical Center. Department of Medicine I ORPHAN Disease Center for Graves' Orbitopathy and Autoimmune Polyendocrinopathy Member, JGU Research Center for Immunotherapy, Mainz, Germany	

15:00–15:50	**Parallel Sessions 2 – Pituitary** Chairs: Dr. Zaina Adnan, Dr. Leonard Seiagh	Hall B
15:00–15:25	**Long Term Management of NFPA** Prof. Yona Greenman | Director, Institute of Endocrinology and Metabolism Tel Aviv–Sourasky Medical Center, Faculty of Medicine, Tel Aviv University	
15:25–15:50	**The Clot Thickens: Thromboembolism in Cushing Syndrome** Prof. Amit Akirov | Endocrine Institute, Rabin Medical Center, Petah–Tikva; Secretary of the Israel Endocrine Society	
15:50–16:00	**Coffee Break & Visit at the Exhibition**	Foyer
16:00–17:30	**Flash Talks Sessions – Presentations from Selected Abstracts**	
16:00–17:30	**Parallel Sessions – Flash Talks** **Adrenal & Bone** Chairs: Dr. Alena Kirzhner, Dr. Elena Chertok Shacham	Hall A
16:00–16:07	**Multicomponent Lateralization Index to Enhance the Accuracy of Adrenal Venous Sampling (AVS) in Primary Aldosteronism Subtyping** Yonit marcus[1], Gabi Shefer[2], Isaack Kori[3], Merav Ingbir[4], Yona Greenman[2], Naftali Stern[5] [1]Institute of Endocrinology, Metabolism and Hypertension, C, [2]Institute of Endocrinology, Metabolism and hypertension, Tel Aviv–Sourasky Medical Center, [3]Interventional Radiology, Department of Imaging, Tel Aviv–Sourasky Medical Center, [4]Department of Internal Medicine, Tel Aviv–Sourasky Medical Center, [5]The Sagol Center for Epigenetics, The Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel	
16:07–16:14	**A Mechanistic Model for the Cortisol Paradox in PTSD** Yaniv Grosskopf[1], Dor Danan[1], Yoav Hayut[1], Yoel Toledano[2], Keren Doenyas–Barak[3], Avi Mayo[1], Uri Alon[1] [1]Department of Molecular Cell Biology, Weizmann Institute of Science, [2]Rabin Medical Center, [3]Shamir Medical Center	

16:14–16:21 **Low Maternal Estriol: Early Indicator of Life–Threatening Adrenal Insufficiency**

Keren Cohen[1], Naomi Weintrob[2], Amir Peleg[3,4], Lena Sagi Dain[3,4], Ilana Koren[1,4]
[1]Pediatric Endocrinology Unit, Lady Davis Carmel Medical Center and Clalit Health Services, Haifa, Israel, [2]The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana Dwek Children Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Isreal 3Genetic Institute, Lady Davis Carmel Medical Center and Clalit Health Services, Haifa, Israel, [4]Ruth and Bruch Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

16:21–16:28 **Optimizing Patient Selection for Adrenal Vein Sampling in Primary Hyperaldosteronism**

Meir Frankel[1], Anthony Verstandig[2], Gavriel Lichewitz[1], Noa Sylvetzky[1], Gabriel Munter[1]
[1]Endocrinology unit, Shaare Zedek Medical Center, affiliated to Faculty of Medicine, Hebrew University, Jerusalem, Israel, [2]Interventional radiology unit, Shaare Zedek Medical Center, affiliated to Faculty of Medicine, Hebrew University, Jerusalem, Israel

16:28–16:35 **Predictive Value of Morning Serum Cortisol for Synacthen Test Outcomes During Corticosteroid Withdrawal**

Leonard Saiegh[1,2], Balsam Dakwar[1], Katya Jovanovic[1], Muaweya Mahamed[3], Hadas Rabani[1], Anan Shalata[1], Emad Khoury[1], Mohammad Sheikh Ahmad[1,2]
[1]Institute of Endocrinology, Bnai Zion Medical Center, Haifa, Israel, [2]The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel, [3]Department of internal medicine B, Bnai Zion Medical Center, Haifa, Israel

16:35–16:42 **Asthma and Stress Fractures in Combat Soldiers: A Nationwide Military Database Study**

Bar Lossos[1,2], Harel Gershgoren[1,2], Idan Levi[1], Maayan Shaked[1], Amit Rimon[1,2], Hadasa Sharshevsky[1], Tomer Talmy[1], Meir Schechter[1,3]
[1]Medical Data Research Institute, Israel Defense Forces Medical Corps, Tel HaShomer, Ramat Gan, Israel, [2]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, [3]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel

16:42–16:49 **Analysis of Clinical Pharmacists` Proactive Intervention for Monitoring and Treating Osteoporosis After Bariatric Surgery**

Sivan Lavi[1], Anna Otcheretianski[1], Gal Omri Orbach[1], Sarah David[1], Daniel Landsberger[1], Inbal Yifrach–Damari[1]
Maccabi Healthcare Services

16:49–16:56 **DXA Screening in Men Aged ≥70 Years: High Burden of Low Bone Density and Favorable Health-Economic Profile in a Real-World Israeli Cohort**

Vanessa Rouach[1,2], Ziv Versano[3], Meital Sasson[3], Yona Greenman[4], Arnon Makori[3], Inbal Goldshtein[5]

[1]Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel, [2]The Dr. Miriam and Sheldon G. Adelson School of Medicine (The Gray School), Tel Aviv University, Israel, [3]Assuta Medical Centers, [4]Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, [5]KI Research Institute

16:56–17:03 **Evaluation of Bone Health After Cancer Diagnosis: Gaps in DXA Assessment and Implications for Clinical Care**

Vanessa Rouach[1,2], Ziv Versano[3], Meital Sasson[3], Yona Greenman[1], Arnon Makori3

[1]Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel, [2]School of Medicine, Faculty of Medical and Health Sciences, [3]Assuta Medical Centers

17:03–17:10 **Comparative Effects of Anti-Osteoporotic Therapies on Mortality Following Hip Fracture: A Real-World Study**

Omri Armoni[1], Itay Pansky[1], Dmitry Shklovsky[2], Uri Yoel[2,3], Merav Fraenkel[2,3]

[1]Goldman School of Medicine, Faculty of Health Science, Ben-Gurion University of the Negev

[2]Endocrinology, Soroka University Medical Center 3Faculty of Health Science, Ben-Gurion University of the Negev

17:10–17:17 **Serum Vitamin D Levels and Functional Recovery After Hip Fracture Rehabilitation: A National Quality Registry-Based Cohort Study**

Limor Friedensohn[1,2], Olga Bronshtein[1], Nethanel Goldschmidt[1]

[1]Quality and Patient Safety Division, Israeli Ministry of Health, [2]Division of Endocrinology, Metabolism and Diabetes, Sheba Medical Center

17:17–17:24 **Assessment of Bone Mineral Density and Trabecular Bone Score in Adolescents and Young Adults with Primary Ovarian Insufficiency**

Noah Gruber[1,2], Shai Bar-Shira[1,2], Myriam Safrai[2,3], Moran Shapira[2,3], Yael Levy-Shraga[1,2]

[1]Pediatric Endocrine and Diabetes Division, Edmond and Lili Safra Children's Hospital, Sheba Medical Center, [2]The Gray Faculty of Medical and Health Sciences, Tel-Aviv University

[3]IVF unit, Department of Obstetrics and Gynecology, Sheba Medical Center

17:24–17:31 **Iron Supplementation and Stress Fractures Risk in 2910 Propensity-Score Matched Female Combatants with Low Ferritin Without Anemia**

Noa Sofer Sali[1], May Merav[1,2], Hadar Sharvit[2]
[1]IDF, [2]The Hebrew University of Jerusalem

16:00–17:30 **Parallel Sessions – Flash Talks** Hall B

Fertility and Gestational Diabetes

Chairs: Dr. Genya Aharon Hananel, Dr. Eran Gershon

16:00–16:07 **Neurochemical Receptor Expression in Ovarian Cells: A Cross-Species Analysis of Neural-Ovarian Communication Pathways**

Mika Colin Trabelsi[1], Anat Kahan[1]
Department of Animal Sciences, The Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem

16:07–16:14 **Earlier Menopause and Risk of Metabolic Dysfunction-Associated Steatotic Liver Disease: A Global Cohort Study**

Joshua Stokar[1], Rivka Dresner-Pollak1
Endocrinology, Hadassah Hebrew University Medical Center

16:14–16:21 **Population-Based Age-Specific Reference Percentiles and Z-Scores for AMH in Women**

Rina Hemi[1], Ronit Machtinger[2,3], Ehud Barhod1, Tomer Ziv[3,4]
[1]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel, Endocrine Laboratory, [2]Department of Obstetrics and Gynecology, Sheba Medical Center, Ramat Gan, Israel, IVF Division, [3]Tel Aviv University, Tel Aviv, Israel, Gray Faculty of Medical & Health Sciences, [4]Tel Aviv University, Tel Aviv, Israel, Baran Department of Epidemiology and Preventive Medicine, School of Public Health

16:21–16:28 **High Prevalence of Poor Sleep and Psychological Distress in a Transgender Clinic Cohort: A Cross-Sectional Study**

Iris Yaish[1], Rivi Tauman[2], Jennifer Zitser Koren[2], Yona Greenman[1]
[1]Endocrine Institute, Tel Aviv Sourasky Medical Center (Ichilov) and Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Sieratzki Sagol institute for Sleep Medicine, TASMC

16:28–16:35 **The Effect of Sex Hormone Priming on LHRH Test Results**

Ilana Koren[1,2] Majd Abu Raia[2], Shadi Ibrahim[3], Hussein Majdoub[3], Inbal Halabi[3], Keren Cohen[3], Shira London[3], Hannah Ludar[3]
[1]Pediatric Endocrinology Unit, Carmel Medical Center, Clalit Health Services
[2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology
[3]Pediatric department, Carmel Medical Center, Clalit Health Services

16:35–16:42 **Continuous Glucose Monitoring Metrics for Predicting Perinatal Outcomes in Women with Type 1 Diabetes Mellitus**

Orit Barenholz[2], Sarit Helman[1], Maayan Bas-Lando, Sorina Grisaru-Granovsky, Ofri Oren

[1]Obstetrics and gynecology, Shaare Zedek medical center, [2]Obstetrics and gynecology, Laniado Medical Center

16:42–16:49 **The Association Between CGM Derived Glycemic Control Measures at Different Gestational Periods Among Women with Pregestational T1D and the Risk of Neonatal Hypoglycemia**

Noam Brakin Lederer[1], Tali Cukierman-Yaffe[1]

Endocrinology, Sheba Medical Center

16:49–16:56 **Moderate Carbohydrate Reduction Is Not Associated with Maternal Ketosis or Adverse Pregnancy Outcomes in Insulin-Treated Pregnancy: Interim Safety Data from a Randomized Controlled Trial**

Naama Shirazi[1,2], Danny Ben-Zvi[1,2], Yoel Toledano[3], Einat Mazor[3], Meital Ron-El[3], Sarit Hellman[4], Maayan Bas Lando[2,4], Karen Hershkop[4], Gil Leibowitz[1,2], Genya Aharon-Hananel[1,2]

[1]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel. [2]Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel, [3]Division of Maternal Fetal Medicine, Helen Schneider Hospital for Women, [4]Medical Center, Petah Tikva, Israel[4] Shaare Zedek Medical Center, Jerusalem, Israel

16:56–17:03 **Breathing New Life into Gestational Diabetes Diagnosis: Pilot Study of a Novel Non-Invasive Breath Test**

Maya Oberman, Tal Schiller[1], Amir Shafat[2], Inbal Avrahami[3], Alena Kirzhner[3], Ziv Tsafrir[3], Edi Vaisbuch[3], Oren Barak[3]

[1]Edith Wolfson Medical Center, [2]School of Pharmacy and Medical Sciences, University of Galway, [3]Kaplan Medical Center

17:03–17:10

Polycystic Ovary Syndrome and Gestational Dysglycemia: A Large Population-Based Cohort Study

Yulia Balmakov[1,2], Orit Pinhas-Hamiel[3,4], Hertzel C Gerstein[5], Gabriel Chodick[6], Maya Nitecki[1,7], Estela Derazne[4], Yael Barer[6], Noah Gruber[8,9], Aya Bardugo[1,2], Cole D. Bendor[1,2], Avi Shina[2], Arnon Afek[10,11], Tali Cukierman-Yaffe[6,12], Adi Vinograd[13,14], Gilad Twig[6,12]

[1]Department of Military Medicine, Faculty of Medicine, Hebrew University Jerusalem, Israel. [2]Israel Defense Forces, Medical Corps, Ramat Gan, Israel. [3]Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel. [4]School of Medicine, Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel. [5]Department of Medicine, McMaster University, Hamilton, Ontario, Canada. [6]Department of Preventive Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Israel. [7]Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, NC, USA. [8]Faculty of Medical and Health Science, Tel Aviv University, Tel Aviv, Israel. [9]Pediatric Endocrinology and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer, Israel. [10]The Dina Recanati School of Medicine, Reichman University, Herzliya, Israel. [11]Central Management, Sheba Medical Center, Ramat Gan, Israel The Dina Recanati School of Medicine, Reichman University, Herzliya, Israel. [12]Division of Endocrinology Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel. [13]The Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel. [14]Department of Epidemiology and Preventive Medicine, School of Public Health, Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv

17:10–17:17 **An Oral Glucose Tolerance Test in Pregnancy and Its Association with Future Cardiovascular Diseases**

Tal Schiller[1,2], Linoy Gabay[3], Oren Barak[4], Alena Kirzhner[5], Edi Vaisbuch[4], Haitham Abu Khadija[6], Gabriel Chodick[7], Yael Barer[2]

[1]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, Institute of Endocrinology, Diabetes and Metabolic Disease, Wolfson Medical Center, [2]Kahn–Sagol–Maccabi Research and Innovation Institute, Maccabi Healthcare Services, Tel Aviv, Israel, [3]Wolfson Medical Center, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel [4]Department of Obstetrics and Gynecology, Kaplan Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, [5]Department of Internal Medicine A, Kaplan Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, [6]Department of Cardiology, Kaplan Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel 7School of Public Health, Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel

16:00–17:30 **Parallel Sessions – Flash Talks** Hall D

Thyroid

Chairs: Dr. Afif Nakhleh, Dr. Elena Itzhakov

16:00–16:07 **Clinical Significance of Infiltrative vs Encapsulated Follicular-Variant Papillary Thyroid Carcinoma: A Questionnaire Study**

Amit Arbel[1], Dania Hirsch[1,2], Amit Ritter[1,3]

[1]Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel, [3]Department of Otolaryngology, Head and Neck Surgery, Rabin Medical Center, Petach Tikva, Israel

16:07–16:14 **Sustained Low-Normal TSH and Risk of Atrial Fibrillation and Vertebral or Hip Fractures**

Afif Nakhleh[3,4], Said Darawshi[1], Ruba Gadban[2]

[1]Clalit Healthcare Services, Northern District, Nazareth, Israel, [2]Department of Internal Medicine D, Rambam Health Care Campus, Haifa, Israel, [3]Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus, Haifa, Israel, [4]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

16:14–16:21 **BRAF and MEK Inhibitors Other Than Dabrafenib and Trametinib for Advanced Thyroid Cancer**

Tzahi Yamin[1], Oded Cohen[1], Eyal Robenshtok[2,3], Inbar Finkel[3,4]
[1]Department of Otolaryngology, Head and Neck Surgery, Assuta Samson Ashdod Medical Center, Ashdod, Israel, [2]Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel, [3]Gray School of Medicine, Tel-Aviv University, Tel-Aviv, [4]Department of Oncology, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel

16:21–16:28 **Prognostic Factors and Survival in Patients with Bone Metastases from Thyroid Cancer**

Noga Odess[1], Liyona Kampel[1,2], Anton Warshavsky[1,2], Gilad Horowitz[1,2], Eyal Robenshtok[1,3], Nidal Muhanna[1,2], Inbar Finkel[1,4]
[1]Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Department of Otolaryngology, Head and Neck and Maxillofacial Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel, [4]Head and Neck Medical Oncology Unit, Division of Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

16:28–16:35 **Inflammatory Biomarkers as Predictors for 90-Day Mortality in Hospitalized Patients with Amiodarone-Induced Thyrotoxicosis – A Historical Cohort Study**

Tali Epstein Weiss[1,2], Tomer Ziv-Baran[3], Eugene Feigin[1,2], Yona Greenman[1,2], Elena Izkhakov[1,2]
[1]Institute of Endocrinology, Diabetes, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv, [3]Department of Epidemiology and Preventive Medicine, School of Public Health, Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

16:35–16:42 **Long-Term Chronic Health Outcomes in CAYA Differentiated Thyroid Carcinoma Survivors and the Impact of Radioactive Iodine Therapy: A Real-World Study**

Rachel Bello Vitrial[1], Michal Yackobovitch-Gavan[1,2], Tal Oron[1,3], Liora Lazar1[,3], Samah Hayek[4]

[1]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel, [2]Gray Faculty for Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, Department of Epidemiology and Preventive Medicine School of Public Health 3Tel Aviv University, Tel Aviv, Israel, Gray Faculty for Medical and Health Sciences, [4]Deptartment of Epidemiology and Preventive Medicine School of Public Health, Gray Faculty for Medical and Health Sciences, Tel Aviv university, Tel Aviv, Israel

16:42–16:49 **Real-World Comparison of the Upcoming ATA 2026 Sonographic Classification with ATA 2015 and ACR TI-RADS in Thyroid Nodules**

Einav Gal Levin[1], Gali Avior[1], Pinchas Klein[2]

[1]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel., Department of Otolaryngology – Head and Neck Surgery, Sheba Medical Center, Technion University, Tel-Aviv, Israel, [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel., Division of Endocrinology, Diabetes, and Metabolism, Sheba Medical Center, Ramat Gan, Israel

16:49–16:56 **Real-World Outcomes of Immune Checkpoint Inhibitor Therapy in Differentiated and Anaplastic Thyroid Carcinoma: A Retrospective Case Series**

Irit Ayalon-Dangur[1,2], Eyal Robenshtok[1,2], Elena Itzhakov[2,3], Liyona Kampel[2,4], Inbar Finkel[2,5]

[1]Institute of Endocrinology, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel, [2]Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [4]Department of Otolaryngology-Head and Neck and Maxillofacial Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [5]Oncology Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

16:56–17:03 **High Early Mortality in Subclinical Hypothyroidism Previously Unrecognized**

David Strrich[1], Ariel israel[2], Rona Lugan[3], Shalom Edri[4], David Gillis[5]
[1]Pediatric Specialists Clinic, Endocrinology and Diabetes, Clalit Health services, and Pediatric endocrinology unit, Shaare Zedek Medical Center, [2]Leumit Research Institute, Leumit Health Services, School of Public Health, Gray Faculty of Medical & Health Sciences, Tel Aviv University, [3]The Eisenberg R&D Authority, Shaare Zedek Medical Center, [4]Health Information Center, Clalit Health Services, Jerusalem, Israel, [5]Department of Pediatrics and Pediatric Endocrinology Unit, Hadassah–Hebrew University Medical Center, Jerusalem, Israel

17:03–17:10 **Daily Goitrogen Intake Does Not Impair Thyroid Function or Lodine Status in Euthyroid Pregnant Women with Mild–to–Moderate Lodine Deficiency: Machine Learning–Based Study**

Yaniv Ovadia[1], Abigail Paradise Vit[2], Simon Shenhav[1,3]
[1]Obstetrics and Gynecology Department, Barzilai University Medical Center, Ashkelon, Israel, [2]Information Systems Department, The Max Stern Yezreel Valley College, Emek Yezreel, Israel, [3]Faculty of Health Sciences, Ben–Gurion University of the Negev, Beersheba, Israel

17:10–17:17 **Close Access to Health Care as a Bridge Overcoming Disparities in Thyroid Cancer**

Oded Cohen[1,2], Larisa Aizikovich[2], Uri Yoel[2,3], Merav Frenkel[2,3], Liroy Caracucli[2]
[1]Otolaryngology, Head and Neck Surgery, Assuta Samson Ashdod, [2]Ben Gurion University, [3]Endocrinology, Soroka Medical Center

17:17–17:24 **Thyroid Cancer in the Elderly– Specific Clinical and Histopathological Characteristics and Treatment Considerations – A Retrospective Cohort Study**

Liroy Caracucli[1], Uri Yoel[4,5], Daphna Idan[1], Natalya Bilenko[2], David Shacham[3,4]
[1]The Goldman Medical School at the Faculty of Health Sciences, Ben–Gurion University of the Negev, Beer Sheva, Israel, [2]Department of Epidemiology, Biostatistics and Community Health Sciences, Ben–Gurion University of the Negev, Beer–Sheva, Israel, [3]Geriatric department, Soroka University Medical Center, Beer–Sheva, Israel, [4]Faculty of Health Sciences, Ben–Gurion University of the Negev, Beer–Sheva, Israel, [5]Endocrinology Unit, Soroka University Medical Center, Beer–Sheva, Israel

16:00–17:30 **Parallel Sessions – Flash Talks** Hall J

Type 1 Diabetes

Chairs: Dr. Marianna Rachmiel, Dr. Miri Stolovich-Rain

16:00–16:07 **Hyperglucagonemia Contribute to the Pathophysiology of Diabetic Kidney Disease by Activating mTOR Signaling in Kidney Proximal Tubule Cells**

Fatema Gamal[1], Aviram Kogot-Lvin[1], Yael Riahi[1], Liad Hinden[2], Erol Cerasi[1], Joseph Tam[2], Gil Leibowitz[1]

[1]Diabetes Unit and Endocrine Service, Hadassah Medical Center of the Hebrew University, Jerusalem, Israel, [2]Obesity and Metabolism Laboratory, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem

16:07–16:14 **Metabolic Determinants of the Diabetogenic Interferon Response in Pancreatic Beta-Cells**

Maya Israeli[1], Shani Peleg[1], Udi Ehud Knebel[1], Chunhua Dai[2], Roni Cohen-Fultheim[3], Benjamin Glaser[1], Erez Y. Levanon[3], Alvin C. Powers[4], Agnes Klochendler[1], Yuval Dor[1]

[1]The Hebrew University of Jerusalem, Israel, [2]Vanderbilt University, Nashville, USA, [3]Bar-Ilan University, Ramat Gan, Israel, [4]VA Tennessee Valley Healthcare, Nashville, TN

16:14–16:21 **Glucosamine Links Hyperglycemia to mTORC1 Activation and Glucose Toxicity in Diabetes**

Ziv Teselpapa[1], Yael Riahi[1], Aviram Kogot-Levin[1], Elisheva Zemelman[1], Fatema Gamal[1], Tamar Cohen[1], Dana Avrahami[1], Erol Cerasi[1], Erez Dror[2], Gil Leibowitz[1]

[1]Diabetes Unit and Endocrine Service, Hadassah Medical Center of the Hebrew University, Jerusalem, Israel, [2]Department of Developmental Biology and Cancer Research, The Institute for Medical Research Israel-Canada (IMRIC), The Hebrew University-Hadassah Medical School, Jerusalem, Israel

16:21–16:28 **RNA Editing Deficiency in Mouse Beta Cells Recapitulates Key Features of T1D Independently of Autoimmunity**

Jonathan Belin[1], Udi Ehud Knebel[1], Shani Peleg[1], Maya Israeli[1], Miri Stolovich-Rain[1], Alvin C. Powers[2,3], Chunhua Dai[2], Heather R. Kates[4], Clive H. Wasserfall[4], MacKenzie Williams[4], Ann Fu[4], Martha Campbell-Thompson[4], Desmond A. Schatz[4], Benjamin Glaser[5], Erez Y. Levanon[6], Agnes Klochendler[1], Yuval Dor[1]
[1]The Hebrew University of Jerusalem, Jerusalem, Israel, [2]Vanderbilt University Medical Center, Nashville, TN, US, [3]VA Tennessee Valley Healthcare, Nashville, TN, USA, [4]College of Medicine, University of Florida, Gainesville, FL, USA, [5]Hadassah Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel, [6]Bar-Ilan University, Ramat Gan, Israel

16:28–16:35 **Three-Dimensional Characterization of Neural–Endocrine Arrangement during Embryonic Development of the Pancreas**

Saada Naim[1], Anna Parnis[1], Nimrod Rotem[1], Nadav Sharon[1]
Faculty of Biology, Technion

16:35–16:42 **Automated, Parallel Single-Nucleus RNA Sequencing of Multiple Pancreatic Islets from a NOD Mouse**

Theophilus Ajiro[1], Anna Parnis[1], Nadav Sharon[1]
Faculty of Biology, Technion – Israel Institute of Technology, Haifa, Israel

16:42–16:49 **A Pilot Study Comparing the Efficacy of Dosing Ultra Rapid Insulin Lispro in a Medtronic 780g Hybrid Closed Loop System at Mealtime or Postmeal**

Roy Eldor[1,2], Eugene Merzon[3,4], Miri Margaliot[1], Tamara Kolitz[1], Assaf Buch[1,4]
[1]Tel Aviv Sourasky Medical Center, [2]Tel-Aviv University,
[3]Leumit HMO, Medical Division, [4]Ariel University

16:49–16:56 **Real-World Teplizumab in Stage 2 Type 1 Diabetes: Safety Signals, Laboratory Kinetics, and Early Glycemic Outcomes in an Eight-Patient Case Series**

Nir Lasman[1], Yair Schwarz[1]
Division of Endocrinology, Diabetes & Metabolism, Sheba Medical Center

16:56–17:03 **The Association Between Baseline Cognitive Function Tests Scores and Physical Capacity in Older People with Type 1 Diabetes Mellitus**

Naama Peltz-Sinvani[1], Hagar Shimon[1], Yasmin Alt[1], Etay Cohen[1], Yael Keler[1], Nir Lasman[1], Jonathan Bleier[1], Amna Jabarin[1], Michal Azmon[1,2], Tali Cukierman-Yaffe[1,3]

[1]The Center for Successful Aging with Diabetes, Division of endocrinology, diabetes and metabolism, Sheba Medical Center, Ramat-Gan, Israel, [2]The Physiotherapy Department, Faculty of Health Sciences, Ariel University, Ariel, Israel, [3]The Epidemiology Department, Gray School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

17:03–17:10 **Prevalence and Outcomes of DKA in Type 1 and Type 2 DM Patients Treated and Not Treated with SGLT-2 Inhibitors**

Elena Chertok Shacham[1,2], Sireen Sharif[3], Rageh Tatoor[4], Snait Ayalon[3]

[1]Medicine, Technion , Israel institute of technology, [2]Endocrinology, Emek medical center, [3]Research authority, Emek medical center, [4]Internal Medicine department A, Emek medical center

17:10–17:17 **Adding Long-Acting Insulin to Automated Insulin Delivery Systems Among Youth with Type 1 Diabetes May Prevent Ketoacidosis Events: A Case Series**

Libby Shopen[1,2], Gila Lavy[1], Shira Harel[3,4], Zohar Landau[4], Shirly Abiri[2,5], Marianna Rachmiel[1,2]

[1]Pediatric Endocrinology and Diabetes Institute, Shamir (Assaf Harofeh) Medical Center, Beer Yaakov, Israel, [2]Grey Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Pediatric Endocrine and Diabetes Unit, Assuta Medical Center, Ashdod, Israel, [4]Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel, [5]Pediatric Endocrinology Unit, Edith Wolfson Medical Center, Holon, Israel

16:00–17:30 **Parallel Sessions – Flash Talks** Hall H

Type 2 Diabetes

Chairs: Dr. Erez Dror, Dr. Talia Diker-Cohen

16:00–16:07 **Diabetic Retinopathy After Liver Transplantation: Impact of Diabetes Type**

Keren Kaminer[1,2], Mor Atlas[3], Talia Diker-Cohen[1,2]

[1]Rabin medical center, Petah Tikva, Israel, [2]Faculty of Medical and Health Sciences, Tel Aviv University, Israel, [3]Business Administration Faculty, Ono Academic College, Kiryat Ono, Israel

16:07–16:14 **Transcriptional Profiling of Functional Beta Cell Heterogeneity**

Alona Volov [1], Aharon Helman[1]
Institute of Biochemistry, Food Science, and Nutrition, The Hebrew University

16:14–16:21 **The Risk of Type 2 Diabetes in Women with Normal Glucose Challenge Test in Pregnancy; Implications for Diabetes Screening and Prevention Strategy**

Yael Barer[1,2], Tal Schiller[2,3], Maya Nitecki[1,4], Gilad Twig[1,5], Gabriel Chodick[1]
[1]Department of Preventive Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, [2]Maccabi Healthcare Services, [3]Institute of Endocrinology, Diabetes and Metabolic Disease, Wolfson Medical Center, [4]Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, NC, USA, [5]Division of Endocrinology Diabetes and Metabolism, Sheba Medical Center

16:21–16:28 **Impaired Glucose Homeostasis in Telomouse, a Novel Mouse Model with Short-Telomeres**

Moshe Sellam[1,2], Kamil Bar-Nes[1,2], Riham Smoom[3], Reut Rifkind[1,2], Benjamin Glaser[2], Yehuda Tzfati[3], Dana Avrahami[1,2]
[1]Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, [2]Department of Endocrinology and Metabolism, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel, [3]Department of Genetics, The Silberman Institute for Life Sciences, The Hebrew University of Jerusalem

16:28–16:35 **Mechanisms of Aldolase B Mediated Beta Cell Glucotoxicity**

Loren Jubran[1,2], Dana Avrahami[1,2], Benjamin Glaser[1]
[1]Department of Endocrinology and Metabolism, Hadassah-Hebrew University Medical Center Jerusalem, Israel, [2]Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

16:35–16:42 **NME3 as a Mediator of the Glucagon–Mitochondria Axis in Hepatic Metabolism and Type 2 Diabetes**

Naama Miron Meir[1], Bar Avni[1], Sonya Basin[1], Kfir Sharabi[1]
The Institute of Biochemistry, Food Science and Nutrition, The Hebrew University of Jerusalem, Israel

16:42–16:49 **The Role of 5-Hydroxymethylcytosine and TET Enzymes in Regulating Beta-Cell Function: A Novel Mechanism in Diabetes Pathogenesis**

Reut Rifkind[1,2], Benjamin Glaser[2], Yuval Dor[1], Dana Avrahami[1,2]

[1]Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, [2]Department of Endocrinology and Metabolism, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Israel

16:49–16:56 **The Effect of Pancreatic Exocrine Replacement Therapy on Diabetic Patients with Pancreatic Exocrine Insufficiency**

Yousef Shukha[1,2], Shadi Hamoud[2,3], Afif Nakhleh[1,4], Naim Shehade[4,5]

[1]Endocrinology, Diabetes, and Metabolism Unit, Rambam Health Care Campus, [2]Internal Medicine E Department, Rambam Health Care Campus, [3]Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, [4]Diabetes and Endocrinology Clinic, Maccabi Healthcare Services, [5]SPHERE Project, The Azrieli Faculty of Medicine, Bar-Ilan University

16:56–17:03 **Clinical Utility of the SARC-F Questionnaire for Assessing Sarcopenia in Community-Dwelling Older Adults with Diabetes and Obesity**

Sharon Barak[1], Roy Eldor[2], Roy Brown[2], Orly Barak[2], Elena Izkhakov[2], Yona Greenman[2], Carla M Prado[3], M. Cristina Gonzalez[4], Assaf Buch[5]

[1]Ariel University, [2]Tel Aviv Sourasky Medical Center, [3]Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada, [4]Federal University of Pelotas, Pelotas, RS, BR, [5]Ariel University; Tel Aviv Sourasky Medical Center

17:03–17:10 **Metformin and Risk of Cancer in Patients with Diabetes Mellitus – A Large – Scale Population Cohort**

Idit Dotan[1,2], Shiri Kushnir[3], Tzippy Shochat[4], Talia Diker Cohen[1,2]

[1]Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Institute of Endocrinology, Diabetes and Metabolism, [2]Tel Aviv University, Tel Aviv, Israel, Gray Faculty of Medical and Health Sciences, [3]Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Research Authority, [4]Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Statistical Consulting Unit

17:10–17:17 **Predictors of Adverse Outcomes in Diabetic Patients Hospitalized with Acute Decompensated Heart Failure**

Alena Kirzhner[1,4], Sheli Rivman[1], Tal Schiller[2,3], Hefziba Green[1,4], Haitham Abu Khadija[1,5], Joshua Friedman[1,4], Ilona Hrechkan[1,4], Saher Jammal[1,4,6]

[1]Faculty of Medicine, The Hebrew University of Jerusalem, [2]Institute of Endocrinology, Diabetes and Metabolic Disease, Wolfson Medical Center, [3]Gray Faculty of Medical and Health Sciences, Tel Aviv University, [4]Department of Internal Medicine A, Kaplan Medical Center, [5]Department of Cardiology, Kaplan Medical Center 6Institute of Pulmonology, Kaplan Medical Center

16:00–17:30 **Parallel Sessions – Flash Talks** Hall I

Extreme Endocrinology: Microbiome, Exercise, Cancer and More

Chairs: Dr. Kfir Sharabi, Dr. Yael Kuperman

16:00–16:07 **Mitigation of Strength-Loss in Aged Mice: Therapeutic Efficacy of Three Compounds**

Gabi Shefer[1], Gilad Lehmann[1], Miguel Morales Moshiashvili[1], Yonit Marcus[1], Yona Greenman[1]

Endocrinology, Tel-Aviv Sourasky Medical Center

16:07–16:14 **The Effects of Gut Microbiome-Derived Metabolites on Hepatic Glucose Metabolism**

Or Maalumi[1], Or Blank[1], Julius Ben-Ari[1], Kfir Sharabi[1]

Biochemistry, Food science and nutrition, Hebrew university of Jerusalem

16:14–16:21 **Mitochondrial Phosphorylation as a Metabolic Switch: The Role of CPS1 in Glucagon-Driven Urea and Glucose Regulation**

Hadar Bar Dagan[1], Yuval Adar[1], Nofar Halimi[1], Kfir Sharabi[1]

Institute of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem

16:21–16:28 **LXRs Participate in the Fasting Response by Assisting C/EBPβ Binding to Enhancers and Promoting the Fasting Transcriptional Program**

Hadar Shalev[1], Tali Gorbonos[1], Maria C. Romero Florian[2], Noga Korenfeld[1], Cigdem Sahin[2], Dana Goldberg[1], Talia Radushkevitz-Frishman[1], Mariana Anosov-Babi[1], Angela Yan[2], Meital Charni-Natan[1], Meirav Bar-Shimon[1], Carolyn L. Cummins[2], Ido Goldstein[1]

[1]The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem. Rehovot, Israel, Institute of Biochemistry, Food Science and Nutrition, [2]Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada

16:28–16:35 **Deciphering liver Glycome Regulation by the PGC-1/FN3K Axis and its Significance**

Neri Minsky[1], Idit Ron-Ronen[1], Efrat Glick-Saar[2], Amir Tirosh[1]
[1]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Sheba Medical Center, [2]Wohl Institute for Translational Medicine, Sheba Medical Center, Sheba Medical Center

16:35–16:42 **Adipose Tissue–Derived FABP4 Promotes Melanoma Growth by Regulating the Tumor Microenvironment Lipidomic Landscape**

Reem Igbaria[1,2], Rinat Livne[1], Amir Tirosh[1,2]
[1]The Dalia and David Arabov Endocrinology and Diabetes Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv University

16:42–16:49 **SDF-1 Mediates Liver Metabolic Adaptation Through CXCR7: Implications for MASH Pathogenesis**

Rachel Barkan Michaeli[1], Chaim Atay Fainshtein[1], Hadar Bar-Dagan[1], Nof Hadar[1], Kfir Sharabi[1]
The Institute of Biochemistry, Food Science, and Nutrition, The Robert H. Smith Faculty of Agriculture, The Hebrew University in Jerusalem

16:49–16:56 **Intense Physical Exercise Induces Acute Hyperglycemia and Hyperinsulinemia in Fasting, Healthy Adults**

Doron Kleiman[1], Rachel Schyr[1], Danny Ben-Zvi[1]
Institute for Medical Research, Israel-Canada, Hebrew University of Jerusalem

16:56–17:03 **Nuclear Receptors Activation Maintains Identity in Primary Mouse Hepatocytes During Culture**

Yael Pelez Daniel[1], Ido Goldstein[1]
The Robert H. Smith Faculty of Agriculture, Food and Environment, Institute of Biochemistry, Food Science and Nutrition. The Hebrew University of Jerusalem

17:03–17:10 **Nutritional Sources of Medium Chain Fatty Acids are Not Required for Ghrelin Acylation in Humans**

Karin Later[1], Rachel Ben-Haroush Schyr[1], Khuloud Abu Tair[2], David Hakimian[3], Danny Ben-Zvi[1,4]
[1]Department of Developmental Biology and Cancer Research, Institute for Medical Research Israel Canada, Hebrew University of Jerusalem, [2]Department of Nutrition and Diet, Hadassah University Medical Center, [3]Institute of Gastroenterology and Liver Disease, Hadassah University Medical Center, [4]Center for Computational Medicine, Hebrew University of Jerusalem

17:10–17:17 **Impact of Standing Desks on Physiological and Psychological Outcomes in Sedentary Office Workers**

Assaf Buch[1,2], Ofer Kis[2], Lani Ofri[1], Odelyah Saad[1], Liat Kulik[3], Roy Eldor[2]
[1]Ariel University, [2]Tel Aviv Sourasky Medical Center, [3]Bar Ilan University

16:00–17:30 **Parallel Sessions – Flash Talks** Hall 5

Obesity

Chairs: **Dr. Liad Linden**, **Dr. Ahmad Khatib**

16:00–16:07 **12:12 Time-Restricted Feeding Corrects Weight Cycling -Induced Aggravation of Glucose Intolerance and Circadian Disruption in Young Mice**

Habib Muallem[1], Alon Zemer[1], Yulia Haim[1], Marina Rosengarten-Levin[1], Yuval G. Noach[1], Alexandra Tsitrina[2], Uri Yoel[1], Hiroshi Tsuneki[3], Tsutomu Wada[3], Toshiyasu Sasaoka[3], Alon Monsonego[4], Assaf Rudich[1]
[1]Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, [2]Ilse Katz Institute of Nanoscale Science and Technology, Ben- Gurion University of the Negev, Beer-Sheva, Israel, [3]Department of Clinical Pharmacology, University of Toyama, Toyama, Japan, [4]The Shraga Segal Department of Microbiology, Immunology and Genetics, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

16:07–16:14 **Higher Prevalence of Short Stature and Excess Weight in Children with Sleep Disorders**

Dr. Inbal Halabi[1], Dana Hadar[2], Hilla Cohen[2], Yardena Tenenbaum Rakover[3], Giora Pillar[4]
[1]Pediatric Endocrine Unit, Carmel Medical Center, Clalit Health Services, [2]Research Authority, Clalit Health Care Organization, Carmel Medical Center, [3]Children's Endocrinology Consulting Center, Clalit Health Services, [4]Sleep Clinic, Clalit Health Services, Technion Faculty of Medicine

16:14–16:21 **Distinct Phenotype of Severe, Treatment-Resistant Obesity Associated with Heterozygous Pathogenic Variants in the Melanocortin Pathway**

Noga Minsky[1,2], Oran Rahamim[3], Odelia Chorin[2,4], Dror Dicker[2,5], Gabriella Segal-Lieberman[1,2]
[1]Division of Endocrinology, Diabetes and Metabolism Sheba Medical Center, Israel, [2]Gray School of Medicine, Tel-Aviv University, Israel, [3]School of Medicine, University of Nicosia, Cyprus, [4]The Danek Gertner Institute of Genetics, Sheba Medical Center 5Internal Medicine, Hasharon Hospital, Israel

16:21–16:28 **Triglyceride–Glucose Index and Risk of End–Stage Liver Disease in Young Adults: A Nationwide Cohort Study**

Michal Kasher Meron[1,2], Tzipi Hornik–Lurie[3], Pnina Rotman–Pikielny[1,2], Gilad Twig[2,4], Tomas Karpati[5]

[1]Endocrinology, Meir Medical Center, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv University, [3]Research, Meir Medical Center, [4]Endocrinology, Sheba Medical Center, [5]Faculty of Sciences and Department of Digital Medical Technologies, Holon Institute of Technology

16:28–16:35 **Teenage Obesity and Incident Cardiovascular Disease in Young Adulthood**

Avishai M. Tsur[1,2], Estela Derazne[3], Arnon Afek[4], Gabriel Chodick[3], Gilad Twig[5,6]

[1]Medical Corps, Israel Defense Forces, [2]Faculty of Medicine, Department of Military Medicine, Hebrew University of Jerusalem, [3]School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University, [4]Dina Recanati School of Medicine, Reichman University, [5]The Institute of Endocrinology Diabetes and Metabolism, Sheba Medical Center, [6]Department of Preventive Medicine and Epidemiology, School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University

16:35–16:42 **Dynamic Life Style–Induced Changes in Asymmetric Dimethylarginine (Adma) Correlate with Alteration in Lipid Profile and Fasting Insulin in Subjects with The Metabolic Syndrome**

Brurya Tal[1], Gabi Shefer[1], Jessica Sack[1], Yonit Marcus[1], Yael Sofer[1], Marianna Yaron[1], Limor Ben Haim[1], Elena Izhakov[1], Yona Greenman[1], Naftali Stern[1]

The Sagol Center for the Metabolic Syndrome, Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv–Sourasky Medical Center; Sackler Faculty of Medicine, Tel Aviv University, Israel

16:42–16:49 **The Role of Sex in Achieving Weight Loss After One Anastomosis Gastric Bypass Surgery**

Ido Sarig[1,2], Wiessam Abu Ahmad[3], Yona Greenman[1,2], **Yael Sofer**[1,2]

[1]Institute of Endocrinology, Sourasky Medical Center, [2]Gray faculty of medical and health sciences, Tel Aviv University, [3]Faculty of Medicine, The Hebrew University of Jerusalem

16:49–16:56 **Adipocyte Hypertrophy in Visceral, Not Subcutaneous, Adipose Tissue Associates Cross-Sectionally with Poor Obesity Phenotype and Predicts Better Response to Bariatric Surgery**

Marina Rosengarten Levin[1,2], Hadar Klein[3], Yulia Haim[1], Alexandra A. Tsitrina[1,4], Habib Mualem[1], Alon Zemer[1], Oleg Zilber[1], Yair Pincu[1], Idit F. Liberty[5], Oleg Dukhno[6], Nur Alkrinawi[6], Iris Shai[3], Assaf Rudich[1], Uri Yoel[1,7]
[1]Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, [2]Maccabi Health Care Services, Rehovot, Israel, [3]The Health & amp Nutrition Innovative International Research Center, Department of Epidemiology, Biostatistics and Community Health Sciences, Faculty of Health Sciences, School of Public Health, Ben-Gurion University of the Negev, Beer Sheva, Israel 4Ilse Katz Institute for Nanoscale Science and Technology, [5]Diabetes Clinic, [6]Surgical word B, [7]Endocrinology, Soroka University Medical Center, Beer-Sheva, Israel

16:56–17:03 **First-Visit Anti-Obesity Medication Recommendation and One-Year Patient Retention and Weight Loss**

Dekel Homossany[1], Michael Rechter[2], Liat Barzilai-Yosef[2], Pnina Rotman-Pikielny[1,2], Michal Kasher Meron[1,2]
[1]Gray Faculty of Medical and Health Sciences, Tel Aviv University
[2]Endocrinology, Meir Medical Center

17:03–17:10 **Exploring Changes in Body Composition and Metabolic Risk in Adolescents with Obesity Under GLP-1 Receptor Agonist Therapy**

Avivit Brener[1,2], Adar Lopez[1], Liat Perl[1,2], Ophir Borger[1], Yael Issan[1], Hagar Interator[1], Eyal Cohen-Sela[1,2], Erez Azoulay[1], Hadar Moran-Lev[2,3], Ronit Lubetzky[2,3], Yael Lebenthal[1,2]
[1]The Institute of Pediatric Endocrinology, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, [2]Gray Faculty of Medical and Health Sciences, Tel Aviv University, [3]The Institute of Pediatric Gastroenterology, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center

17:10–17:17 **A deflection Points During Weight Loss: Call for Identification and Action**

Brurya Tal[1], Gabi Shefer[1], Jessica Sack[1], Yonit Marcus[1], Yael Sofer[1], Marianna Yaron[1], Limor Ben Haim[1], Yona Greenman[1], Naftali Stern[1]
The Sagol Center for the Metabolic Syndrome, Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center; Sackler Faculty of Medicine, Tel Aviv University, Israel

Thursday, July 16, 2026

07:30–08:30	**Registration, Refreshments & Visit the Exhibition**	Foyer
08:30–10:00	**Parallel sessions – Oral Presentations from Selected Abstracts**	
08:30–10:00	**Parallel Sessions – Abstracts** **Pituitary and NETs** Chairs: **Prof. Amit Akirov**, **Dr. Meir Frankel**	Hall A

08:30–08:42 **Identifying Transcription Factor Programs Responsible for Pituitary Stem Cell Differentiation into Gonadotropes in the Neonate Using Single-Cell Multiomics**

Gil Golan[1], Daniel Sheridan[2], Karine Rizzoti[2], Robin Lovell-Badge[2], Philippa Melamed[1]

[1]Faculty of Biology, Technion-Israel Institute of Technology, [2]Francis Crick Institute

08:42–08:54 **Higher Panomen-3 Grade Predicts the Need for Additional Interventions Following Surgery in Patients with Non-Functioning Pituitary Macroadenomas**

Efrat Markus[1,2], Yaron Rudman[2,3], Genady Drozdinsky[2,4], Ilan Shimon[2,3], Shlomit Koren[1,2]

[1]Endocrine and Diabetes Institute, Shamir Medical Center, [2]Gray Faculty of Medical & Health Sciences, Tel Aviv University, [3]Institute of Endocrinology, Beilinson Hospital, Rabin Medical Center, [4]Infectious Diseases Unit, Beilinson Hospital, Rabin Medical Center

08:54–09:06 **Immune Checkpoint Inhibitor-Related Hypophysitis: Tel Aviv Sourasky Medical Center Cohort**

Ruti Karov[1], Esther Osher[1,2], Yona Greenman[1,2]

[1]Endocrinology Metabolism And Hypertension, Tel Aviv Souraski Medical Center, [2]Faculty Of Medicine, Tel-Aviv University

09:06–09:18 **Proximal Gastric Endocrine Cells are Long-Lived and Follow a Unique Developmental Trajectory**

Amit Elad[1], **Michelle Malis**[1], Yifaa Friedman[1], Rachel Ben-Haroush Schyr[1], Danny Ben-Zvi[1,2]

[1]Developmental Biology and Cancer Research, Hebrew University of Jerusalem [2]Center for Computational Medicine, Hebrew University of Jerusalem

09:18–09:30 **ProGRP as a Biomarker in Lung Carcinoids Associated with DIPNECH**

Anat Bel-Ange[2], Benjamin Nisman[1], Ofra Maimon[3], Hovav Nechushtan[3], Nir Peled[4], Veronika Denysova[2], Simona Ben-Haim[5], Karin Atlan[6], Ori Wald[7], David Gross[2], Tamar Peretz[1], Simona Grozinsky-Glasberg[2]
[1]Department of Oncology, Hadassah and Hebrew University Medical Center, Jerusalem, Israel, [2]Neuroendocrine Tumor Unit, ENETS Center of Excellence, Division of Internal Medicine, Hadassah Medical Center, Jerusalem, Israel, [3]Israel Sharett Institute of Oncology, Hadassah Medical Center, Jerusalem, Israel, [4]The Institute of Oncology, Shaarei Zedek Medical Center, Jerusalem, Israel, Jerusalem, Israel, [5]Department of Nuclear Medicine & Biophysics, Hadassah Medical Organization, Israel. Faculty of Medicine, Hebrew University of Jerusalem, Israel, Jerusalem, Israel, [6]Department of Pathology, Hadassah Medical Organization, Jerusalem, [7]Department of Cardiothoracic Surgery, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

09:30–09:42 **Mitotic Count and Ki-67 Index in Gastroenteropancreatic Neuroendocrine Neoplasms: Concordance Analysis and Association with Metastatic Disease**

Mohammad Sheikh Ahmad[1,2], Abed Agbarya[2,3], Sharon Talisman[1,2], Jacob Bejar[4], Hila Kreizman Shefer[4], Monica Laniado[2,5], Leonard Saiegh[1,2]
[1]Institute of Endocrinology, Bnai Zion Medical Center, Haifa, Israel, [2]The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel, [3]Institute of Oncology, Bnai Zion Medical Center, Haifa, Israel, [4]Institute of Pathology, Bnai Zion Medical Center, Haifa, Israel, [5]Department of Surgery, Bnai Zion Medical Center, Haifa, Israel

08:30–10:00 **Parallel Sessions – Abstracts** Hall B

Thyroid

Chairs: Dr. Liat Barzilai-Yosef, Dr. Michal Gershinsky

08:30–08:42 **Successful Levothyroxine Discontinuation in Patients with a Persistently Normal TSH**

Ori Adler[1], David Fisher[2,3], Tamar Freud[4], Howard Tandeter[4], Merav Fraenkel[2,3]
[1]Internal Medicine B, Soroka University Medical Center, [2]Endocrinology, Soroka University Medical Center, [3]Faculty of Health Science, Ben Gurion University of the Negev, [4]Department of Family Medicine and Siaal Research Center for Family Medicine and Primary Care, Ben-Gurion University of the Negev

08:42–08:54 **Pregnancy Outcomes by Thyroid Autoantibody Status in Euthyroid and Subclinical Hypothyroid Women– Insights from a Nationwide Cohort Study**

Maya Maimon Solomon[1], Uri Yoel[2], Yuval Elhayani[3], Nitzan Burrack[3], Merav Fraenkel[2], Tamar Eshkoli[1]

[1]Department Of Gynecology, Soroka Medical Center, [2]Department of Endocrinology, Soroka Medical Center, [3]Clinical Research Center, Ben Gurion University

08:54–09:06 **Second Primary Malignancies Among Pediatric and Young Adult Survivors of Differentiated Thyroid Cancer: Real-World Evidence**

Rachel Bello Vitrial[1], Michal Yackobovitch-Gavan[1,2], Liora Lazar[1,3], Samah Hayek[2]

[1]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel, [2]Deptartment of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel 3Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

09:06–09:18 **Efficacy and Safety of RFA Therapy in Patients with Benign Thyroid Nodules Compared to Other Modalities**

Roni Mechorish[1], Moshe Yehuda[1,2], Eyal Robenshtok[1,3], Hadar Duskin-Bitan[1,3], Gideon Bachar[1,2], Ilan Shimon[1,3], Ido Amir[1,2]

[1]Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Department of Otolaryngology, Head and Neck Surgery, Rabin Medical Center, Petach Tikva, Israel, [3]Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel

09:18–09:30 **Does the Difference Between Bethesda V and VI Predict Long Term Outcomes of Thyroid Cancer?**

Marina Ioffe[1], Anna Anna Hochner-Ger[2], Ignat Schwartz[2], Reut Halperin[3], Galit Avior[4], Pinchas Klein[1,5]

[1]Division of Endocrinology, Diabetes and Metabolism, The Chaim Sheba Medical Center, Tel Hashomer, Israel, [2]Institute of Pathology, The Chaim Sheba Medical Center, Tel Hashomer, Israel, [3]ENTIRE – Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Diabetes and Metabolism, The Chaim Sheba Medical Center, Tel Hashomer, Israel, [4]Otolaryngology Head& Neck Surgery Department, The Chaim Sheba Medical Center, Tel Hashomer, Israel, [5]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

09:30–09:42 **Clinical Characteristics and Outcomes of Thyrotoxicosis in Amiodarone–Treated Individuals with Prior Hypothyroidism**

Afif Nakhleh[1,2], Limor Adler[3,4], Shirley Shapiro Ben David[3,4], Daniella Rahamim–Cohen[3], Ori Liran[3,4], Sagit Zolotov[1,2]

[1]Diabetes and Endocrinology Clinic, Maccabi Healthcare Services, Haifa, Israel, [2]Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus, Haifa, Israel, [3]Health Division, Maccabi Healthcare Services, Tel Aviv, Israel, [4]Faculty of Medicine, Tel Aviv University, Israel

09:42–09:54 **The Impact of Severe Overt Primary Hypothyroidism on Outcomes of Hospitalized Patients with Bacteremia**

Dor Eldar[1], Naftali Gross[2], Meir Frankel[1], Eli Ben–Chetrit[3], Gabriel munter[1]

[1]Endocrinology, Diabetes & Metabolism Unit, Shaare Zedek Medical Center, Hebrew University School of Medicine, [2]Internal medicine Division, Shaare Zedek Medical Center, Hebrew University School of Medicine, [3]Infectious Diseases Unit, Shaare Zedek Medical Center, Hebrew University School of Medicine

08:30–10:00 **Parallel Sessions – Abstracts** Hall D

Gestational Diabetes & Metabolism

Chairs: Prof. Hilla Knobler, Dr. Alex Gorshtein

08:30–08:42 **Chronic Intermittent Hypoxia Induces a KLF5–Dependent Shift toward Lipid Oxidation and Glucose Intolerance**

Eden Engal[1,2], Hadas Masury–David[2], Naama Lopiansky[1,2], Shirel Fradkov[1,2], Liran Brodsky[1,2], Saja Baraghithy[6], Joseph Tam[6], Xue Sun[3], Oren Ram[3], Asaf Marco[4], Rinat Abramovitch[1,2], Alex Gileles–Hillel[1,5]

[1]Faculty of Medicine, Hebrew University of Jerusalem, [2]The Wohl Institute for Translational Medicine, Hadassah Medical Center, [3]Silberman Institute of Life Sciences, Hebrew University of Jerusalem, [4]Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem, [5]The Wohl Institute for Translational Medicine; Department of Pediatrics, Hadassah Medical Center [6]Obesity and Metabolism Laboratory , School of Pharmacy, Faculty of Medicine, the Hebrew University of Jerusalem

08:42–08:54 **A Pilot Randomized Controlled Trial of Low–Versus Standard– Carbohydrate Diets in Women with Gestational Diabetes Mellitus: Effects on Maternal Ketone Levels, Glycemic Control, and Obstetric Outcomes**

Kim Goldberg–Politzer[1], Assaf Buch[2,3], Tomer Avnon[4,5], Shiraz Vered[6], Roni Elran–Barak[1], Daniela Saunyama[2,3,] Roy Eldor[3,4], Yariv Yogev[4,5], Marianna Yaron[3,4]

[1]School of Public Health, University of Haifa, Haifa, Israel, [2]Department of Nutritional Sciences, School of Health Sciences, Ariel University, Ariel, Israel, [3]Institute of Endocrinology, Diabetes, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [4]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, [5]Lis Hospital for Women's Health, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [6]Department of Statistics, University of Haifa, Haifa, Israel

08:54–09:06 **The Association Between CGM Derived Glycemic Control Measures at Different Gestational Periods Among Women with Pregestational T1D and the Risk of LGA**

Yael Keler[1], Tali Cukierman–Yaffe[1]

Institute of Endocrinology and Diabetes, Sheba Medical Center

09:06–09:18 **Paternal Ketogenic Diet Programs Offspring Liver Metabolism and Physical Activity**

Miri Stolovich–Rain[1], Jamie Magrill[1], Saja Baraghithy[2], Rachel Ben–Haroush Schyr[1], Elad Ben–Cnaan[2], Evgenia Volinsky[3], Danny Ben–Zvi[1], Benjamin Glaser[4], Joseph Tam[2], Yuval Dor[1]

[1]Faculty of Medicine, Department of Developmental Biology and Cancer Research, Hebrew University of Jerusalem, Institute for Medical Research Israel–Canada, [2]School of Pharmacy, Obesity and Metabolism Laboratory, Hebrew University of Jerusalem, Institute for Drug Research, [3]Endocrinoligy and Fertility lab, Shaare Zedek Medical Center, [4]Endocrinology and Metabolism Service, Hadassah University Hospital

09:18–09:30 **Overweight, Obesity, and All–Cause Illness–Attributed Workdays Loss in a Nationwide Cohort of 481,067 Young Adults**

Bar Lossos[1,3], Bar Weinstein[1,2], Jacob Megreli[1,3], Ma'ayan Shaked[1,3], Zivan Beer[1,3], Doron Yaya–Stupp[1,3], Meir Schechter[1,4]

[1]Medical Data Research Institute, Israel Defense Forces Medical Corps, Tel HaShomer, Ramat Gan, Israel, [2]School of Mathematical Sciences, Tel Aviv University, Tel Aviv, Israel, [3]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, [4]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel

09:30–09:42 **A Biphasic Fetal Growth Response to Maternal Diabetes is Driven by Fetal β-Cell Plasticity and Reshaped by a Ketogenic Diet**

Omer Cohenshtam[1], Aharon Helman[1], Amnon Zung[1]
Department of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem, Rehovot, Israel

08:30–10:00 **Parallel Sessions – Abstracts** Hall H

Type 2 Diabetes

Chairs: Prof. Amir Tirosh, Dr. Hadar Duskin-Bitan

08:30–08:42 **Epigenetic Adaptation of Beta Cells Across Lifespan and Disease: Age-Related Demethylation is Advanced in Type 2 Diabetes**

Dana Avrahami Tzfati[1], Elisabetta Manduchi[2,3], Hélène C. Descamps[2,3], Klaus H. Kaestner[2,3], Jinping Liu[2,3], Jonathan Schug[2,3], Benjamin Glaser[4], Ali Naji[5]
[1]Department of Developmental Biology and Cancer Research, Hadassah Medical school, Hebrew University, Jerusalem, Israel, [2]Institute of Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [3]Department of Genetics, University of Pennsylvania, Philadelphia, PA, [4]Department of Endocrinology and Metabolism, Hadassah Medical Center, Faculty of Medicine, Hadassah Medical Center, Hebrew University of Jerusalem, Israel, [5]Department of Surgery and Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

08:42–08:54 **Beta Cells Intrinsically Sense and Limit Their Secretory Activity via mTORC1-RhoA Signaling**

Saar Krell[1], Aharon Helman[1]
The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem

08:54–09:06 **Explainable AI for Personalized Prediction of Adherence to Drug Therapy in People with Type 2 Diabetes: A Nationwide Retrospective Cohor**

Michal Kasher Meron[1,2], Riad Taher[3,4], Adi Berliner[4], Eitan Bachmat[5], Doron Levinson[5]
[1]Endocrinology, Meir Medical Center, [2]Gray Faculty of medical and Health Sciences, Tel Aviv University 3Endocrinology, Rambam Medical Center, [4]Clalit Health Services, [5]Department of Computer Science, Ben-Gurion University

09:06–09:18 **Intensive Versus Conventional Hyperglycemic Control in Hospitalized Non-Critically Ill Patients, a Multicenter, Randomized Control Trial**

Irit Ayalon-Dangur[1,2], Michal Michaelis[3], Irina Genin[4], Maya Arlyuk[4], Tzippy Shohat[5], Lichay Kaufman[4], Noam Shira Darnell[4], Tal Shapira[6], Leonard Leibovici[2,7], Yaron Rudman[1,2], Maly Keler[8], Ronit Koren[2,8], Jen Hojman[8], Mogher Khamaisi[9], Said Darawshi[9,10], Marco Bertolotti[11], Yonatan Shneor Patt[12], Ran Abuhasira[13,14], Idit F Liberty[14,15], Nuphar Vinegrad1[4,15], David Fischer[14,15], Kim Ben Tikva Kagan[16], Alon Grossman[2,4]

[1]Institute of Endocrinology, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel, [2]Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Department of Internal Medicine E, Rabin Medical Center, Petah Tikva, Israel, [4]Department of Internal Medicine B, Rabin Medical Center, Petah Tikva, Israel, [5]Bio-statistical institute, Rabin Medical Center, Beilinson Campus, Israel, [6]Department of Internal Medicine D, Rabin Medical Center, Petah Tikva, Israel, [7]Research Authority, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel, [8]Department of Internal Medicine A, Shamir Medical Center, Zerifin, Israel, [9]Clalit health services, north district, Israel, [10]Department of Internal Medicine D, Rambam Health Care Campus, Haifa, Israel, [11]Department of Biomedical, Metabolic and Neural Sciences, Unit of Geriatric Medicine University of Modena and Reggio Emilia, University Hospital of Baggiovara, Modena, Italy, [12]Department of Internal Medicine B, Sheba Medical Center, Tel-Hashomer, Israel, [13]Clinical research center, Soroka University Medical Center, Beer-Sheva, Israel, [14]Faculty of health sciences, Ben Gurion University of The Negev, Beer-Sheva, Israel, [15]Diabetes Clinic, Soroka University Medical Center, Beer-Sheva, Israel, [16]Department of Internal Medicine A, Rabin Medical Center, Petah Tikva, Israel

09:18–09:30 **Neurodegeneration Onset with Glucagon-Like Peptide-1 Receptor Agonists in People with Type 2 Diabetes: Aa Real-World Multinational Cohort Study**

Meir Schechter[1,2], Alisa Fishkin[1,2], Ofri Mosenzon[2,3], Dvora R Sehtman-Shachar[1,2], Tali Cukierman-Yaffe[4,5], Gil Leibowitz[1,2], Genya Aharon-Hananel[1,2]

[1]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel, [2]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, [3]Regeneron Pharmaceuticals Inc., New York, New York, USA, [4]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel, [5]Department of Epidemiology and Preventive Medicine, School of Public Health, Dear Gray Faculty of Medical and Health Sciences, Tel-Aviv University, Tel Aviv, Israel

09:30–09:42 **Delayed Puberty and Type 2 Diabetes Risk**

Orit Pinhas-Hamiel[1,2], Maya Simchoni[3,4], Estela Derazne[5], Cole D. Bendor[4,5], Avishai M. Tsur[5,6], Adi Vinograd[7,8], Miri Lutski[7,8], Inbar Zucker[5,9], Vibha Singhal[10], Hertzel C. Gerstein[11], Arnon Afek[12], Amir Tirosh[5,13], **Gilad Twig**[13,14]

[1]Pediatric Endocrine and Diabetes Division, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, [2]Department of Medicine, Gray Faculty of Medical & Health Sciences university, [3]Department of Military Medicine, Hebrew University, Jerusalem, [4]The Israel Defense Forces Medical Corps, Ramat Gan, Israel, [5]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, [6]Department of Medicine, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel, [7]The Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel, [8]Department of Epidemiology and Preventive Medicine, School of Public Health, Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israe, [9]The Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel, [10]Division of Endocrinology, Department of Pediatrics, University of California, Los Angeles, CA, USA, [11]Department of Medicine, McMaster University, Hamilton, Ontario, Canada, [12]The Dina Recanati School of Medicine, Reichman University, Israel, [13]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel Hashomer, Israel, [14]Department of Epidemiology and Preventive Medicine, School of Public Health., Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

09:42–09:54 **Association Between Adherence to Inpatient Diabetes Care Guidelines and Hospitalization Complications: A Multicenter Real-World Study**

Shahar Oded[1], Yuval Shahar[1], Erez Shalom[1], Amir Bashkin[2,3], Leonard Saig[4,5], Dror Cantrell[6], Irit Wirsansky[7], Muhamad Badarne[2,8], Irena Barash[9], Avivit Cahn[10,11], Irit Hochberg[4,7]

[1]Medical Informatics Research Center, Ben Gurion University, Be'er Sheva, Israel, [2]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel, [3]Endocrinology and Diabetes unit, Galilee Medical Center, Naharia, Israel, [4]Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel, [5]Endocrinology Institute, Bnai Zion Medical Center, Haifa, Israel, [6]Internal Medicine Department C, Shamir Medical Center, Be'er Ya'akov, Israel, [7]Endocrinology Unit, Hillel Yaffe Medical Center, Hadera, Israel, [8]Endocrinology and Diabetes Service, Tzafon Medical Center, Ramat Poriya, Israel, [9]Internal Medicine C, Barzilai Medical Center, Ashkelon, Israel, [10]Internal Medicine Department A, Hadassah Ein Kerem, Jerusalem, Israel, [11]Faculty of Medicine, Hadassah Hebrew University Hospital, Jerusalem, Israel

10:00–10:30	**Coffee Break & Visit at the Exhibition**	Foyer
10:30–11:15	**Parallel Sessions 3 – Sex Hormones** Chairs: **Dr. Gal Omry**, **Dr. Sigal Shaklai**	Hall A
10:30–10:55	**Physiology of Menopause and Puberty from Millions of Lab Tests** **Prof. Uri Alon** | The Weizmann Institute of Science, Rehovot	
10:55–11:15	**Gender-Affirming Medicine in Israel, 2026** **Dr. Iris Yaish** | Director, Transgender Health Center, Tel Aviv Medical Center	
10:30–11:15	**Parallel Sessions 3 – Neuroendocrine Tumors** Chairs: **Prof. Simona Glasberg**, **Dr. Nariman Saba Khazen**	Hall B
10:30–10:55	**Neuroendocrine Tumors in Women: Special Considerations During Pregnancy** **Prof. Martyn Caplin** | DM FRCP, Professor of Gatsroenterology & Neuroendocrine Cancer, Royal Free Hospital, London	
10:55–11:15	**GLP-1 Receptor Agonists and Neuroendocrine Tumors: Navigating Risk in Clinical Practice** **Dr. Orit Twito** | Head of Endocrinology and Diabetes Unit, Wolfson Medical Center, Holon **Dr. Anat Bel Ange** | Neuroendocrine Tumor Unit, ENETS Center of Excellence, Hadassah Medical Center, Jerusalem	
10:30–11:15	**Parallel Sessions 3 – Diabetes–What are the Big Questions in Basic Research?** Chair: **Dr. Ron Piran**	Hall D
10:30–10:55	**Panel: What are the Big Questions in the Basic and Translational Diabetes Research?** Moderator: **Dr. Ron Piran** | The Azrieli Faculty of Medicine, Bar-Ilan University, Israel **Prof. Klaus Kaestner** | School of Medicine, University of Pennsylvania, Philadelphia, PA, USA **Prof. Gil Leibowitz** | Hadassah Diabetes Unit, Department of Endocrinology, Hadassah Medical Center, Jerusalem **Prof. Yuval Dor** | Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem **Dr. Nadav Sharon** | Faculty of Biology, Technion, Israel institute of technology, Haifa **Prof. Limor Landsman** | Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv	

10:55–11:15 **Mapping the Battlefield of Autoimmune Diabetes, One Islet at a Time**
Dr. Nadav Sharon | Faculty of Biology, Technion, Israel institute of technology, Haifa

11:20–12:05 **Plenary Session 3** Hall B
Chair: Prof. Amit Tirosh

11:20–12:05 **Advances in Neuroendocrine Tumors**
Prof. Martyn Caplin | DM FRCP, Professor of Gatsroenterology & Neuroendocrine Cancer, Royal Free Hospital, London

12:05–13:00 **Parallel Sessions 4 – Hot Topics in Endocrinology** Hall A
Chairs: Dr. Shlomit Koren, Dr. Lior Tolkin

12:05–12:20 **Recent Updates in Adrenal Diseases**
Dr. Mohammad Sheikh-Ahmad | Institute of Endocrinology, Bnai Zion Medical Center, Israel. The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa

12:20–12:40 **Milestones and Recent Breakthroughs in the Treatment of Elevated Triglycerides**
Dr. Hofit Cohen | Lipid service director, The Bert W. Strassburger Lipid Center, Sheba Medical Center, Tel-Hashomer, Israel. Gray School of Medical Sciences, Gray Faculty of Medical and Health Sciences, Tel Aviv University

12:40–13:00 **Social Physiology: Glucose Homeostasis is More Efficient in Social Proximity**
Prof. Shir Atzil | Department of Psychology, The Hebrew University of Jerusalem, Jerusalem

12:05–13:00 **Parallel Sessions 4 – Obesity: Childhood and Adults** Hall B
Chair: Prof. Avivit Cahn

12:05–12:35 **Panel: Does History of Obesity Affect Obesity Treatment?**
Moderator: Prof. Avivit Cahn
Prof. Gilad Twig | The Division of Endocrinology Diabetes and Metabolism, Sheba Medical Center, Ramat Gan
Dr. Liya Kerem | Pediatric Endocrinology Unit, Head of the Multidisciplinary Clinic for Childhood and Adolescent Obesity, Hadassah Medical Center, The Hebrew University of Jerusalem, Jerusalem
Dr. Zvi Perry | Senior Surgeon and Professor of Surgery, The bariatric Unit, and the surgical research unit, Department of General Surgery A, Soroka University Medical Center, Beer-Sheva

12:35–13:00 **Regulatory Measures to Reduce Obesity**
Dr. Irit Hochberg | Endocrinology Unit, Hillel Yaffe Medical Center, Hadera

13:05–13:50 **Satellite Lunch's & visit at the Exhibition**

13:05–13:50 **Satellite Lunch – The Pancreas at the Metabolic Crossroads: The Interplay Between Diabetes, Obesity, and Digestive Enzymes** Hall H
Sponsored by: **Abbott**

This Session Highlights the Pancreas as a Central Hub Connecting Diabetes, Obesity, Bariatrics, and Advanced Pharmacologic Treatments with Exocrine Function. We will Explore how Pancreatic Exocrine Insufficiency Shape Metabolic Outcomes, Influence Patient Symptoms, and Affect Treatment Success
Dr. Idit Dotan | Head of Diabetes Unit, Head of the Multidisciplinary Center for Obesity Treatment and the Bariatric Surgery Unit, Rabin medical Center, Beilinson campus
Dr. Liat Barzilay–Yoseph | Specialist in Internal Medicine, Endocrinology and Diabetes, Endocrinology Unit, Meir Medical Center
Ms. Rotem Rafaeli | Dietitian Specializing in Bariatrics and Obesity Treatment, the Multidisciplinary Center for Obesity Treatment and the Bariatric Surgery Unit, Rabin medical Center, Beilinson Campus

13:05–13:50 **Satellite Lunch – Unmasking Silent Atherosclerosis: The Role of Imaging in Early Detection and Risk Management** Hall I
Sponsored by: **Sanofi**

Unmasking Silent Atherosclerosis: The Role of Imaging in Early Detection and Risk Management
Prof. Sa'ar Minha | Director of Interventional Cardiology, Shamir Medical Center. Chairman, Interventional Cardiology Working Group, Israel Heart Society

13:05–13:50 **Satellite Lunch – OSA Beyond the Airway: Cardiometabolic Insights and Clinical Integration in Obesity Care** Hall J
Sponsored by: **Eli Lilly**

13:05–13:30 **Metabolic Implication of OSA and its Treatment**
Prof. Avivit Cahn | Director, Internal Medicine Department A, Hadassah Ein Kerem. Chair, National Council of Diabetes and Obesity. Chair, Israeli Diabetic Foot and Wound Healing Society

13:30–13:50 **The Obesity, Sleep Apnea and Cardiovascular Axis**
Prof. Avishay Grupper | Director of the Heart Failure Unit, Shamir Medical Center

13:50–14:20	**Posters Exhibition & Lunch**	Foyer
14:20–15:05	**Plenary Session 4** Chair: Dr. Uri Yoel	Hall B
14:20–15:05	**The Landscape of Treatment of Thyroid Eye Disease** Prof. George Kahaly | Professor of Medicine and Endocrinology/Metabolism Johannes Gutenberg University (JGU) Medical Center. Department of Medicine I ORPHAN Disease Center for Graves' Orbitopathy and Autoimmune Polyendocrinopathy Member, JGU Research Center for Immunotherapy, Mainz, Germany	
15:05–17:15	**Prize Session – IES Awards** Chairs: Prof. Merav Fraenkel | President, Israel Endocrine Society; Head of Endocrine Service, Soroka University Medical Center, Faculty of Health Science, Ben-Gurion University of the Negev, Beer-Sheva, Israel Prof. Amit Akirov | Endocrine Institute, Rabin Medical Center, Petah-Tikva; Secretary of the Israel Endocrine Society	Hall B
15:05–15:20	**Updates from Last Year's IES Research Grants Awardees** Dr. Anat Bel-Ange, Dr. Alena Kirzhner	
15:20–15:30	**The Chowers Award** | Dr. Regev Landau	
15:30–15:50	**The Lindner Award** | Prof. Danny Ben-Zvi	
15:50–16:10	**Best Mentors Award** | Dr. Yoel Toledano, Prof. Yehiel Zick	
16:10–16:20	**Best Community Physician Award** | Dr. Ahmad Khatib	
16:20–16:30	**The Uri Liberman Award for Life Long Achievement** | Prof. Yael Levy-Shraga	
16:30–16:40	**The Uri Liberman Award in Bone and Minerals Research for Young Researchers** | Dr. Michal Kasher Meron	
16:40–16:50	**Best Abstracts**	
16:50–17:05	**Closing Remarks**	
17:20–18:20	**Introduction Meeting only for Participants of the Exam Preparation Course (Room 5)** Dr. Hadar Duskin Bitan | Dr. Amir Bashkin	

CKD- Chronic Kidney Disease; SZC- Sodium Zirconium Cyclosilicate; RAASi- Renin Angiotensin Aldosterone System inhibitors; 1.Lokelma MOH approved prescribing information; 2.Spinowitz BS, et al. *Clin J Am Soc Nephrol.* 2019;14(6):798-809; 3.Diabetes Care. 2026;49(Supplement_1):S246-S260. doi:10.2337/dc26-S011

לפני מתן מרשם יש לעיין בעלון לרופא כפי שאושר על ידי משרד הבריאות https://www.gov.il/he/pages/hbs2026 המלצות הועדה הציבורית להרחבת סל שירותי הבריאות – עדכון 2026

once weekly

mounjaro®

KwikPen®
(tirzepatide) injection

A Lilly Medicine

TOGETHER, REACHING WEIGHT LOSS GOALS IS POSSIBLE[1]

Actor portrayals. Not actual patients or healthcare providers.

Mounjaro provides:

GIP/ GLP-1

A novel of mechanism of action[1]:
The **first-and-only approved treatment** activating both **GIP and GLP-1** receptors to target the pathophysiology of obesity.

-23.6 kg

Significant weight loss[1]:
Participants taking Mounjaro 15 mg **significantly reduced their body weight** by an average of 23.6 kg (22.5%).*†

Improvements in key cardiometabolic parameters[2]:
Improvements demonstrated in **systolic blood pressure, diastolic blood pressure, waist circumference, triglycerides, HDL cholesterol,** and **LDL cholesterol.**‡

-63%

Significant reduction in OSA severity[3]:
Patients with moderate to severe OSA and obesity taking Mounjaro **reduced the severity of their condition by up to -62.8%**‡¶

Continuous efficacy with or without PAP [3]:
Clinically significant reductions in AHI were observed with Mounjaro in studies with patients who did or did not use PAP therapy‡¶

הצטרפו למהפכה
בטיפול במחלת ההשמנה

לחצו כאן

INDICATION:
Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
in addition to other medicinal products for the treatment of diabetes.
For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.
Weight management
Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m2 (obesity) or
- ≥ 27 kg/m2 to < 30 kg/m2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

For trial results with respect to obstructive sleep apnoea (OSA) in adults with obesity, see section 5.1.

REFERENCES:

1. Mounjaro Summary of Product Characteristics as approved by Israeli MOH
2. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038.
3. Malhotra A, et al. N Engl J Med 2024; 391(13): 1193-205.

Lilly
A MEDICINE COMPANY

OZEMPIC®

עכשיו הזמן להתחיל מוקדם יותר

הרחבת הזכאות בסל הבריאות עבור מטופלים עם HbA1c בין 6.5-7.5% עם BMI≥25

בנוכחות מחלה נלווית אחת* לאחר טיפול
בשתי תרופות פומיות

אוזמפיק® מגן על ה**כליות**, על ה**לב** ועל ה**חיים**
של חולי הסוכרת עם CKD, **ומתועדף באיזון הגליקמי וההפחתה במשקל**[1,2]

*מחלה נלווית:
מחלת לב - כלילית, מחלה סרברווסקולרית, מחלת כליה כרונית, מחלת כלי דם פריפרית.

CKD, Chronic Kidney disease
The information presented is based on the FLOW study and is consistent with the approved label. Semaglutide 1 mg (Ozempic) is indicated for the treatment of adults with insufficiently controlled T2D as an adjunct to diet and exercise.
Kidney composite outcome included: onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes.

References:
1. Perkovic et al. N Engl J Med 2024;391:109-121.
2. American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2025. Diabetes Care. 2025 Jan 1;48(1 Suppl 1):S27-S49.

For complete information please refer to the **updated physician leaflet** in the MOH website.
For information on the **approved product's indications, most common adverse events**, and **significant warnings**, enter the following link: Ozempic aPI / scan the QR code

Need additional information? Contact the Marketing Authorization Holder at: www.novonordisk.co.il

ONCE-WEEKLY OZEMPIC® semaglutide injection

IL26OZM00012

novo nordisk®

Help People with obesity

LIVE LIGHTER™

with Wegovy®

Wegovy®

The First and Only

anti obesity medication

Proven to **treat obesity** and **reduce the risk of major cardiovascular events**
in patients with ASCVD without T2D[1,2]

Included in the **National Health Basket** for **adolescents**[3*]

*Wegovy® is included is the national health basket for weight management in adolescents ages 12 years and above with obesity (BMI ≥95th percentile as defined on sex-and age- specific BMI growth charts) and body weight above 60 kg.
The treatment must be accompanied by a structured professional follow-up program that includes medical and nutritional monitoring.
Initiation of therapy will be carried out based on a prescription issued by a specialist in endocrinology, pediatric endocrinology, or a specialist working in a dedicated obesity-management clinic.

MACE, major cardiovascular events; T2D, type 2 diabetes; ASCVD, Atherosclerosis Cardiovascular Disease
MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.
Wegovy® is included in the national health basket for adolescent aged 12 years and above with BMI≥95 percentile ((based on CDC growth charts)) and body weight above 60 kg, as an adjunct to a reduced-calorie diet and increased physical activity for weight management.

References:
1. Lincoff AM, et al. N Engl J Med. 2023; ;389:2221-2232.
2. Wegovy® IL SPC as approved by MOH.
3. Director General's Directive, ministry of health. Published March 8, 2026. Access March 8, 2026. https://www.gov.il/BlobFolder/policy/mtr01-2026/he/files_circulars_mtr_mtr01-2026.pdf

For complete information please refer to the **updated physician leaflet** in the MOH website.
For information on the **approved product's indications, most common adverse events**, and **significant warnings**, enter the following link: Wegovy aPI / scan the QR code

Need additional information? Contact the Marketing Authorization Holder at: www.novonordisk.co.il

wegovy®
semaglutide injection 2.4 mg

IL26SEMO00047

novo nordisk®

מדיסון שמחה לעדכן לגבי כניסה לסל הבריאות 2026 של המוצרים Crysvita ו-Evenity

(Burosumab) Crysvita
נכנסה לסל עבור חולי TIO
(Tumor-Induced Osteomalacia)

לראשונה, חולים עם TIO, אשר אצלם לא ניתן לבצע הסרה מלאה של הגידול, יוכלו לקבל טיפול המכוון ישירות לגורם האנדוקריני של המחלה המאפשר לכליות להשיב את היכולת לספוג זרחן חזרה לדם.

Crysvita הוא הטיפול הראשון המנטרל את עודף ההורמון FGF23 ובכך מאפשר ספיגה מחדש של זרחן ע"י הכליות, נרמול רמתו בדם ושיפור משמעותי במדדי המחלה. הטיפול מוביל ל:

- הפחתה משמעותית במדדי רככת העצם
- ריפוי שברים ומניעת שברים חדשים
- שיפור התפקוד הגופני
- הפחתת כאבים ועייפות
- שיפור ניכר במדדי איכות החיים

הנחיות מינון ל-TIO במבוגרים (מגיל 18 ומעלה):
מינון התחלתי מומלץ:
0.5 מ"ג/ק"ג כל 4 שבועות
(מעוגל ל-10 מ"ג הקרובים ביותר)
אפשרות העלאת מינון:
עד 2 מ"ג/ק"ג, עד למנה מקסימלית של 180 מ"ג כל שבועיים

Evenity (Romosozumub) נכנסה לסל הבריאות כקו ראשון לחולי אוסטאופורוזיס בסיכון גבוה

קו טיפול ראשון למטופלות פוסטמנפאוזליות המצויות בסיכון גבוה מאוד לשבר, אשר עברו שבר אחד לפחות בשנתיים האחרונות עם צפיפות עצם נמוכה מ-2.5- (t score)[1]

בנוסף להתוויות הקיימות[2]

קו טיפול שני כאשר חלה הידרדרות משמעותית במצב במהלך טיפולים אחרים (כולל ביספוספונאטים במתן פומי או תוך וריד או רלוקסיפן) המוגדרת כאחת מאלה:

1. שבר אוסטיאופורוטי
2. הרעה מובהקת במדידות חוזרות של צפיפות העצם [לפחות 5%, בעמוד השדרה או בירך (total hip)]

במהלך מחלתו החולה יהיה זכאי לקבל טיפול בשני קורסים טיפוליים בתכשירים אנאבוליים

Indications:
EVENITY is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
For full details please refer to the PI as approved by the IL MoH.
License Holder: Amgen Europe B.V., Israel Branch
שם בעל הרישום: אמג'ן יורופ בי.וי., ישראל
ISR-785-26-80003

EVENITY (romosozumab)injection

AMGEN
שם בעל הרישום: אמג'ן יורופ (בי.וי., ישראל

For full details please refer to the Israeli PI as approved by the MoH

References:
1. חוזר מנכל משרד הבריאות לשנת 2026
2. The Israeli drug registry | 3. Imanishi Y et al. Interim Analysis of a Phase 2 Open-Label Trial Assessing Burosumab Efficacy and Safety in Patients With Tumor-Induced Osteomalacia. J Bone Miner Res. 2021 Feb;36(2):262-270. | 4. Jan de Beur SM, et al. Burosumab Improves Patient-Reported Outcomes in Adults With Tumor-Induced Osteomalacia: Mixed-Methods Analysis. J Bone Miner Res. 2023 Nov;38(11):1654-1664. | 5. Prescribing Information, Ministry of Health (IL)

MEDISON

XLH0077

ZOOM IN
Focused on your Experiences

Conference Secretariat
Tel: +972-3-5209002
2 Nirim St. Tel Aviv 6706037
www.ZoomInPro.co.il

ABSTRACTS

106

Real-world Safety of Romosozumab in High Cardiovascular Risk Patients

Joshua Stokar[1,2], Auryan Szalat[1,2]
[1]*Departments of Medicine & Endocrinology, Hadassah Medical Center*
[2]*Faculty of Medicine, The Hebrew University of Jerusalem*

Introduction:

Use of Romosozumab for treatment of osteoporosis is hindered by a black box regulatory warning regarding an increased risk for major adverse cardiovascular (MACE). We previously demonstrated that romosozumab was not associated with increased MACE in patients without recent cardiovascular (CV) events; however, data on its safety in individuals with recent CV events remain limited.

Objective:

To compare 1-year cardiovascular risk following initiation of romosozumab versus parathyroid hormone (PTH) analogues in patients with documented recent acute CV events prior to therapy.

Methods:

Using TriNetX, a global federated electronic health record network, we identified adults who initiated romosozumab or a PTH analogue (abaloparatide or teriparatide) after experiencing an acute myocardial infarction or cerebral infarction within the preceding year. Propensity-score matching (PSM) generated 702 patients per cohort, balanced across 54 demographic, clinical, medication, and laboratory variables. Outcomes were assessed from day 1 to day 365 post-index. The primary endpoint was incident 3-point MACE (3P-MACE): acute myocardial infarction, acute stroke, or death. Secondary endpoints included myocardial infarction, cerebrovascular events, acute heart failure, and all-cause mortality. Hazard ratios (HRs) were calculated using Cox proportional hazards models.

Results:

During 1-year follow-up, romosozumab was not associated with excess cardiovascular risk compared with PTH analogues. Event counts and hazard ratios (HR [95% CI]) for romosozumab vs PTH analogues were: 3P-MACE: 293 vs 321; HR 0.94 (0.80–1.10); Myocardial infarction: 72 vs 84; HR 0.88 (0.65–1.21); Acute heart failure: 31 vs 38; HR 0.84 (0.52–1.35); CVA or TIA: 222 vs 238; HR 0.97 (0.81–1.16); Death: 30 vs 44; HR 0.72 (0.45–1.14)

Conclusions:

Among patients with recent major cardiovascular events, romosozumab was not associated with an increased risk of cardiovascular events or mortality compared with PTH analogues. These real-world findings support the cardiovascular safety of romosozumab even in patients at very high baseline cardiovascular risk, challenging the conclusions derived from the ARCH trial.

107

Autoimmune Disease Prevalence in Ethiopian versus Non-Ethiopian Type 1 Diabetes Patients in Israel

Alena Kirzhner[1,2], Amir Bashkin[3,4], Hefziba Green[1,2], Haitham Abu Khadija[2,5], Ramon Cohen[2,6], Meital Zikry Deitch[2,7], Tal Schiller[8,9]

[1]*Department of Internal Medicine A, Kaplan Medical Center*
[2]*Faculty of Medicine, Hebrew University of Jerusalem*
[3]*Department of Diabetes, Endocrinology and Metabolism, Galilee Medical Center*
[4]*Azrieli Faculty of Medicine, Bar-Ilan University of Safed*
[5]*Department of Cardiology, Kaplan Medical Center*
[6]*Department of Internal Medicine B, Kaplan Medical Center*
[7]*Intensive care unit, Kaplan Medical Center*
[8]*Department of Diabetes, Endocrinology, and Metabolic disease, Wolfson Medical Center*
[9]*Faculty of Medicine, Tel Aviv University*

Objective: The prevalence of autoimmune diseases (AIDs) in Ethiopian patients with type 1 diabetes (T1D) is mainly unknown. This study aimed to determine the co-occurrence of AIDs in T1D Ethiopian patients and to compare their prevalence to non-Ethiopian Israeli patients.

Methods: A cohort, retrospective analysis of 12,759 T1D patients, of whom 672 (5.3%) were of Ethiopian descent, aged ≥18 years, registered in the Clalit Health Services database was conducted. The AIDS cases were identified by ICD-10 codes from 2000 to 2023. Additionally, data on thyroid peroxidase antibody (TPO) and tissue transglutaminase (TTG) antibodies were extracted and analyzed.

Results: The mean age of the entire cohort was 30.4±18.9, 54% were male, and the mean follow-up was 10.9±6.1 years. An additional AID was diagnosed among 14% of the Ethiopian and 26% of the non-Ethiopian populations (p0.001). Although the prevalence of coexisting autoimmune conditions was approximately half in the Ethiopian group, the relative distribution pattern of common and less common AIDs remained similar to that observed in the non-Ethiopian population.

Conclusion: The prevalence of AIDs in Ethiopians is lower than in non-Ethiopian patients with T1D, indicating the existence of ethnic differences in susceptibility to AID. Nevertheless, the low screening rates highlight the need for greater vigilance and adherence to guidelines by medical staff.

108

Ibuprofen Therapy for Ghosal Hematodiaphyseal Dysplasia: Report of Two Affected Brothers

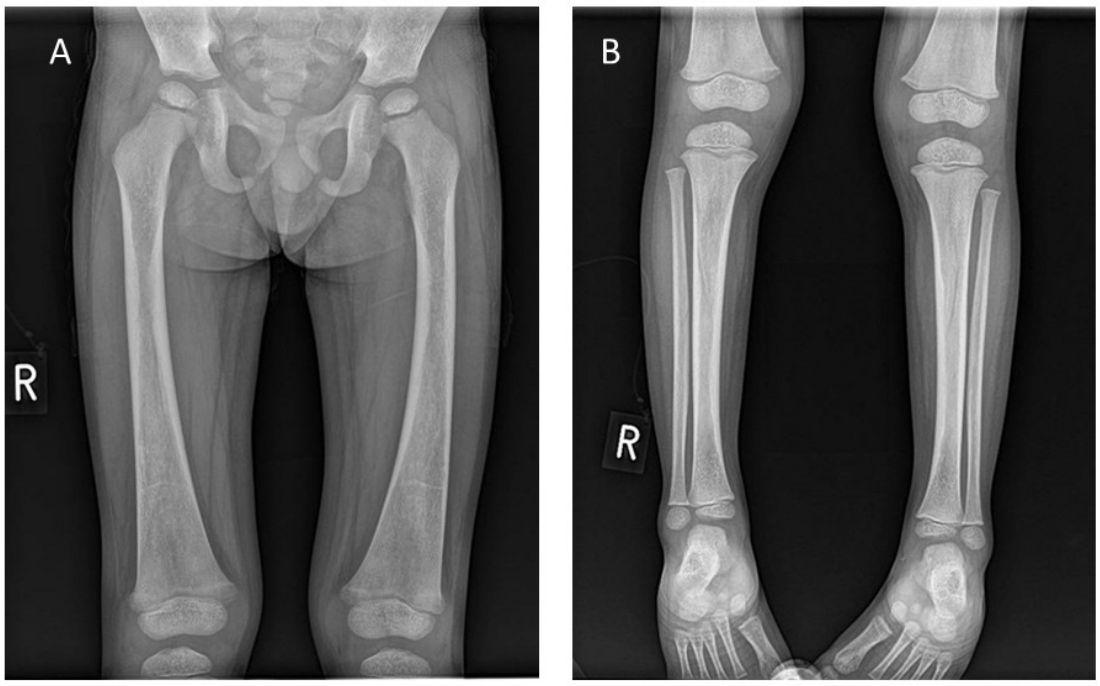
Sarah Malkiel[1,2], Einat Shalev-Goldman[2,3], Etai Adam[1,2], **Yael Levy-Shraga**[2,3]
[1]*Division of Pediatric Hematology and Oncology, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center*
[2]*Faculty of Medical and Health Sciences, Tel Aviv University*
[3]*The institute for Pediatric Endocrinology and Diabetes, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center*

Background: Ghosal hematodiaphyseal dysplasia (GHDD) is a rare autosomal recessive disorder characterized by diaphyseal bone thickening and progressive anemia, caused by pathogenic variants in the TBXAS1 gene encoding thromboxane A synthase 1. Nonsteroidal anti-inflammatory drugs (NSAIDs), by inhibiting COX-1 and COX-2 in the prostaglandin–thromboxane pathway, may mitigate hematologic and skeletal manifestations by modulating downstream effects of impaired thromboxane metabolism.

Aim: To describe hematologic and skeletal responses to ibuprofen therapy in two brothers with GHDD.

Case Presentation: We report two siblings with genetically confirmed GHDD born to first-degree cousins. The first patient, a 4-year-8-month-old boy, developed anemia at 6 months of age and required blood transfusions every 1–2 months. He also experienced recurrent leg pain. Bone marrow biopsy demonstrated hypocellular marrow with fibrosis and trabecular thickening. Skeletal survey revealed mildly increased bone density and bilateral undertubulation of the femora. Whole-exome sequencing identified a homozygous TBXAS1 variant (c.605GA, p.Trp202Ter). Ibuprofen therapy was initiated following diagnosis. Since then, he has remained transfusion-free for nine months, with improved hemoglobin levels, though skeletal and abdominal pain persist. The second patient, his 6-year old brother, exhibited a milder disease course, presenting with mild anemia at 18 months of age without transfusion requirement, along with intermittent bone pain. Bone marrow biopsy likewise demonstrated hypocellularity. He began ibuprofen therapy seven months ago and has since maintained stable hemoglobin levels. Both brothers are scheduled for repeat skeletal evaluation to assess changes in the skeletal findings.

Conclusion: Ibuprofen therapy in these two siblings with GHDD was associated with hematologic improvement and transfusion independence. Given the central role of diaphyseal hyperostosis and skeletal pain in GHDD morbidity, longitudinal assessment of skeletal outcomes is essential. These cases highlight the need for further studies to clarify the therapeutic impact of NSAIDs on the skeletal dysplasia component of GHDD.



109

Effectiveness of a multimodal monitoring system in improving care and outcomes for diabetes patients with peripheral artery disease following lower limb revascularization

Sara Promislow[1], Chen Speter[2], Orly Tamir[3]
[1]*Israeli Center for Diabetes Research and Policy, Sheba Medical Center*
[2]*Vascular Surgery, Sheba Medical Center*
[3]*Israeli Center for Diabetes, Sheba Medical Center*

Background: The lower limb amputation rate in diabetes patients in Israel is one of the highest among high to moderate income countries. The integrated patient unit (IPU) was established at the Sheba Medical Center to address this issue. The IPU has a unique monitoring system for patients with diabetic foot ulcers who undergo revascularization to restore blood flow and promote healing, including remote digital monitoring, a wound clinic, and periodic ultrasound exams. Study Aim: This study accompanied the IPU digital remote and on-site monitoring system to evaluate its effectiveness in improving postoperative care and outcomes for diabetes patients following revascularization. Methods: Between June 2023 and July 2024, 107 cases of diabetic foot ulcers among 94 patients underwent revascularization and enrolled in postoperative monitoring. Data was collected from patient records and the hospital database at baseline and every 3 months, up to 12 months after the procedure. Patient and staff satisfaction with the system was evaluated via interviews. Data was analysed using descriptive statistics and qualitative analysis methods. Results: Of the 107 cases, 78.5% were among male patients, at a mean age of 74.64 years (SD 9.58) with diabetes for a mean of 21.39 years (SD 11.56). By the end of 12 months, among the 107 cases followed, we recorded 16 deaths (15%), 29 major amputations (27%), 6 worsened wound status (5.6%), 4 improved wound status (3.7%), 43 healed wounds (40%), and 5 lost to follow up (4.6%). Remote digital wound monitoring was used at least once in more than half of the cases followed (65%, n=70), mainly in the first 3 months, where a mean of 4.87 (SD 7.44) instances occurred. Patients who used the system were highly satisfied with these interactions; however, no significant correlation was found between remote wound monitoring and improvement in wound status at 3 months. A statistically significant correlation was found between face-to-face clinic visits and routine ultrasound testing and positive wound outcomes by the end of 12 months. Significant improvements were found in blood perfusion at 3 and 6 months and pain levels across time. No significant difference was found in health services use between the 12 months prior to and the 12 months after revascularization. Conclusions: The remote monitoring system provided support to patients who engaged in such interactions and may have contributed to improving their quality of life; however, in-person clinic visits and ultrasound exams were crucial to a positive outcome.

110

Can pharmacist-led monitoring improve compliance with safety measures in long-term bisphosphonate therapy

Shereen Shalabi Habshe[1], Orly Shimoni[2], Uri Goldwasser[3], Merav Fraenkel[4,5]
[1]*M.Sc. in Clinical Pharmacy, Faculty of Health Sciences, Ben-Gurion university of the Negev.*
[2]*Clinical Pharmacology, Soroka University Medical Center*
[3]*Goldman School of Medicine, Faculty of Health Science, Ben Gurion University of the Negev*
[4]*Endocrinology, Soroka University Medical Center*
[5]*Facutly of Health Science, Ben-Gurion University of the Negev*

Background:

Bisphosphonates are first-line therapy for osteoporosis, but long-term use requires regular monitoring of renal function, serum calcium and vitamin D, and bone mineral density (BMD) to ensure safety and efficacy. This study evaluated patterns of clinical and laboratory follow-up among long-term bisphosphonate users in a large community setting.

Methods:

A retrospective observational study was conducted using electronic health records from Clalit Health Services, Southern District. Patients ≥50 years treated with oral bisphosphonates for a minimum of 6 months per treatment year or with zoledronic acid at least once yearly between 2002–2024 were included. Individuals were stratified by cumulative treatment duration:

Results:

A total of 15,333 patients met inclusion criteria mean age at treatment initiation was 70.5±9.1 years and 86.5% were female. Treatment duration distribution was:

Conclusions:

Substantial gaps exist between osteoporosis guideline recommendations and real-world monitoring of long-term bisphosphonate therapy, with adherence deteriorating markedly as treatment duration increases. The absence of structured oversight places patients at avoidable risk for serious complications. A pharmacist-integrated monitoring model, with access to key laboratory and DXA data through existing clinical information systems, could enable continuous surveillance, early detection of deviations, and proactive intervention.

112

Analysis of Clinical Pharmacists` Proactive Intervention for Monitoring and Treating Osteoporosis After Bariatric Surgery

Sivan Lavi[1], Anna Otcheretianski[1], Gal Omri Orbach[1], Sarah David[1], Daniel Landsberger[1], Inbal Yifrach-Damari[1]
Maccabi Healthcare Services

Background

Bariatric surgeries, particularly malabsorptive procedures, are a recognized risk factor for osteoporosis. According to the position statement of the American Society for Metabolic and Bariatric Surgery, bone mineral density (BMD) testing should be performed in patients who have undergone malabsorptive bariatric surgeries at baseline and approximately two years postoperatively. Injectable bisphosphonates are considered the preferred therapeutic option in this population.

Objectives

To evaluate follow-up and treatment patterns among patients after bariatric surgeries, and to implement clinical pharmacists` interventions aimed at optimizing primary and secondary prevention of osteoporosis. Additionally, to raise physicians` awareness regarding the inclusion of patients with “malabsorption” in the approved indications for BMD testing under the national health basket.

Methods

Recommendations for monitoring, screening, and treating osteoporosis in bariatric patients were developed, along with an informational document for clinicians, based on literature review and expert opinion.
An interventional project targeted two cohorts aged 50 and older:

Group 1: Patients who underwent malabsorptive surgery in 2020–2021 without prior BMD testing
Group 2: Patients who underwent malabsorptive surgery in 2011–2023, listed in the osteoporosis registry without pharmacologic treatment for osteoporosis.
Clinical pharmacists proactively contacted physicians to promote appropriate follow-up and treatment.

Results

A total of 627 and 325 patients met intervention criteria in Groups 1 and 2, respectively.

At least one additional risk factor for impaired bone health, beyond bariatric surgery, was documented in 27% of patients, qualifying for BMD referral at any age.

Post-intervention, BMD referrals were issued for 45% of patients in both groups.

In Group 2, treatment was prescribed for 22% of patients, and 17% purchased the medication.

Vitamin D testing was ordered for 76% of all patients.

The intervention prompted development of a dynamic “patient journey” within the nutrition department, incorporating automated alerts for patients lacking timely BMD testing or presenting with low vitamin D levels.

Conclusions

Targeted pharmacist-led interventions significantly improved adherence to recommended monitoring and treatment protocols in bariatric patients at risk for osteoporosis.

Furthermore, proactive engagement with approximately 600 physicians helped reduce knowledge gaps.

These findings highlight the need to establish clear guidelines for medical teams regarding monitoring, screening, and treatment of osteoporosis in bariatric patients, and to include malabsorptive bariatric surgery as a formal indication for BMD testing referral within the national health basket.

113

A Biphasic Fetal Growth Response to Maternal Diabetes is Driven by Fetal β-Cell Plasticity and Reshaped by a Ketogenic Diet

Omer Cohenshtam[1], Aharon Helman[1], Amnon Zung[1]
Department of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment,, Hebrew University of Jerusalem, Rehovot, Israel.

Aims/hypothesis

Maternal diabetes confers various risks to fetal growth, leading to macrosomia in mild cases but often causing intrauterine growth restriction (IUGR) in severe cases. The mechanisms governing these opposite responses are poorly understood, specifically in light of the intimate regulation of insulin by glucose, and the fetal growth signaling induced by insulin We hypothesized that the degree of maternal hyperglycemia dictates a biphasic fetal pancreatic response that determines fetal growth, and that a nutritional intervention with a ketogenic diet could modify this outcome.

Methods

We used the Insulin-rtTA;TET-DTA mouse model to induce preconception diabetes. Dams were stratified into control, mild diabetes (glucose range 175-300 mg/dl), and severe diabetes (glucose 300 mg/dl) groups and maintained on either a standard chow or ketogenic diet. We assessed fetal growth, serum C-peptide, and performed ex-vivo islet functional assays. Fetal pancreata were analyzed by immunohistochemistry for β-cell area, proliferation, maturation, and mTORC1 activity.

Results

On a chow diet, mild maternal diabetes induced fetal macrosomia, that was driven by β-cell hyperplasia, hyperinsulinemia, and β-cell premature functional maturation. This was associated with a strong activation of the mTORC1 pathway and upregulation of the MAF BZIP Transcription Factor A (MAFA). In contrast, severe diabetes caused IUGR associated with reduced β-cell mass and profound functional impairment due to glucotoxicity. The ketogenic diet had divergent effects: it successfully normalized fetal growth in the mild diabetes group by preventing β-cell proliferation and premature maturation, subsequently reducing insulin secretion. However, it failed to rescue IUGR in the severe diabetes group, despite partially restoring β-cell function. Notably, the ketogenic diet disrupted the correlation between fetal insulin and body weight, revealing a primary, insulin-independent, growth-restrictive effect.

Conclusions/interpretation

Fetal growth in diabetic pregnancy is dictated by a biphasic β-cell response to maternal glycemic environment, which is orchestrated at a molecular level by the mTORC1 pathway. A ketogenic diet can prevent macrosomia both by reducing β-cell stimulation and through insulin-independent mechanisms, but it cannot reverse established IUGR, highlighting the complex and sometimes contradictory effects of nutritional interventions during diabetic pregnancies.

114

Growth Hormone/IGF/Growth factors, Pediatric endocrinology

Introduction of Somatrogon in Pediatric Growth Hormone Deficiency: Real-World Insights from A National Survey of Pediatric Endocrinologists

Eyal Cohen-Sela[1,2], Asaf Oren[1,2], Liat Perl[1,2], Ravit Regev[1,2], Anat Segev Becker[1,2], Ori Eyal[1,2], Kineret Mazor-Aronovitch[2,3], Ariel Tenenbaum[2,4], Marianna Rachmiel[2,5], Yael Lebenthal[1,2], Avivit Brener[1,2]

[1]*The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

[2]*Gray School of Medicine, Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel*

[3]*Pediatric Endocrine and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Ramat Gan, Israel*

[4]*The Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*

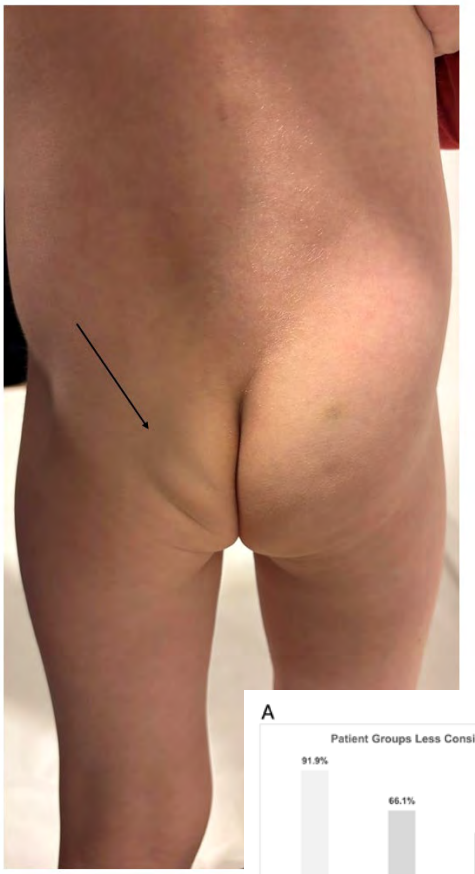
[5]*Pediatric Endocrinology and Diabetes Institute, Shamir (Assaf Harofeh) Medical Center, Beer Yakov, Israel*

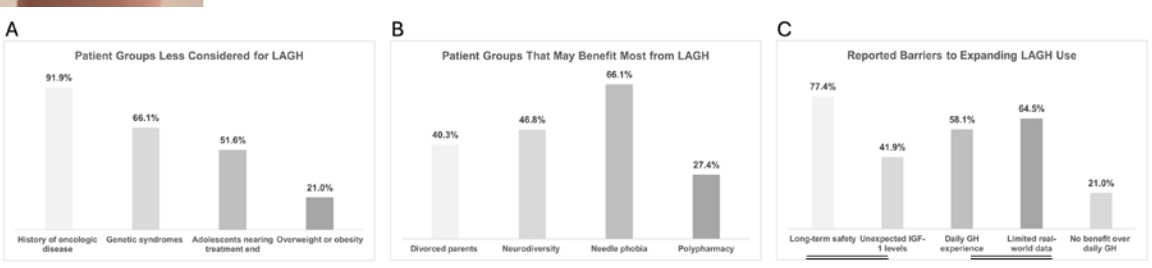
Objective: To characterize real-world prescribing patterns, perceived barriers, and clinician attitudes toward the recently introduced (July 2024) promising long-acting growth hormone (LAGH) somatrogon for treating pediatric growth hormone deficiency in Israel.

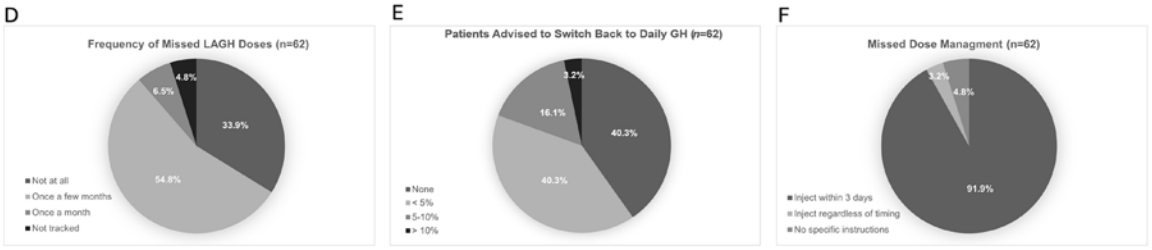
Methods: A nationwide survey was conducted between May and June 2025 among 102 pediatric endocrinologists. The structured 19-item questionnaire queried treatment prevalence, patient selection, dosing strategies, monitoring practices, and physician concerns regarding long-term safety.

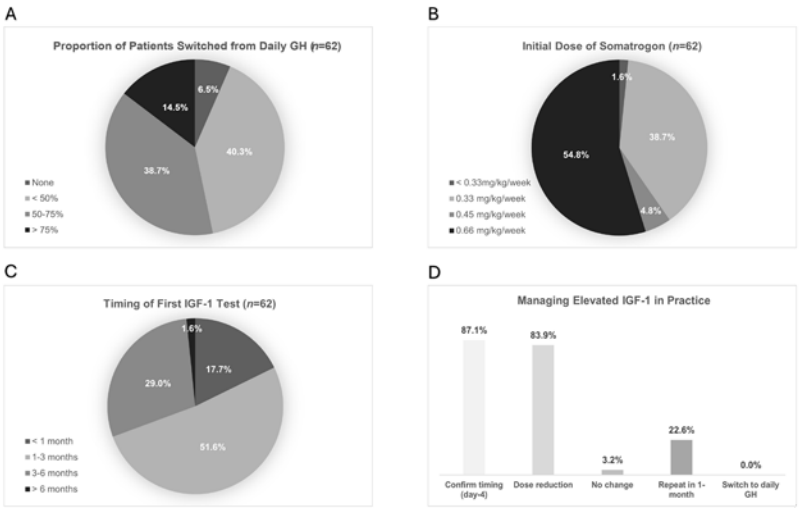
Results: Sixty-five pediatric endocrinologists responded (63.7% response rate), collectively reporting somatrogon treatment in at least 874 patients. Thirty-three respondents (50.8%) reported that they had transitioned over one-half of their patients from daily growth hormone therapy. The most common initial somatrogon dose was 0.66 mg/kg/week (54.8%), with the remaining physicians administered lower starting doses. Specifically, most of the physicians (91.9%) were reluctant to prescribe somatrogon for patients with an oncologic history or genetic syndromes (66.1%). Long-term safety concerns were the primary barrier to broader adoption (77.4%). Injection site reactions comprised the most frequently reported adverse effect (62.9%); marked injection site lipoatrophy was reported in one case, following repeated administration of injections into the same region. Reversion to daily therapy were recalled by 59.7% of the respondents, typically representing isolated cases within each physician’s practice.

Conclusions: This survey revealed heterogenous LAGH prescribing behaviors among pediatric endocrinologists during the introductory period of its availability. The findings call for continued search for real-world evidence and refined clinical guidelines to promote effective and safe integration of this promising therapy into clinical practice.




A
Patient Groups Less Considered for LAGH
91.9%
66.1%
51.6%
21.0%
History of oncologic disease
Genetic syndromes
Adolescents nearing treatment end
Overweight or obesity
B
Patient Groups That May Benefit Most from LAGH
40.3%
46.8%
66.1%
27.4%
Divorced parents
Neurodiversity
Needle phobia
Polypharmacy
C
Reported Barriers to Expanding LAGH Use
77.4%
41.9%
58.1%
64.5%
21.0%
Long-term safety
Unexpected IGF-1 levels
Daily GH experience
Limited real-world data
No benefit over daily GH


D
Frequency of Missed LAGH Doses (n=62)
4.8%
6.5%
33.9%
54.8%
Not at all
Once a few months
Once a month
Not tracked
E
Patients Advised to Switch Back to Daily GH (n=62)
3.2%
16.1%
40.3%
40.3%
None
< 5%
5-10%
> 10%
F
Missed Dose Managment (n=62)
3.2%
4.8%
91.9%
Inject within 3 days
Inject regardless of timing
No specific instructions


A
Proportion of Patients Switched from Daily GH (n=62)
6.5%
14.5%
40.3%
38.7%
None
< 50%
50-75%
> 75%
B
Initial Dose of Somatrogon (n=62)
1.6%
38.7%
54.8%
4.8%
< 0.33mg/kg/week
0.33 mg/kg/week
0.45 mg/kg/week
0.66 mg/kg/week
C
Timing of First IGF-1 Test (n=62)
1.6%
17.7%
29.0%
51.6%
< 1 month
1-3 months
3-6 months
> 6 months
D
Managing Elevated IGF-1 in Practice
87.1%
83.9%
3.2%
22.6%
0.0%
Confirm timing (day-4)
Dose reduction
No change
Repeat in 1-month
Switch to daily GH

Parathyroid, bone and calcium metabolism, Pediatric endocrinology, Other

An AI-assisted Tool for Automated Growth Monitoring in Pediatric Achondroplasia

Eyal Cohen-Sela[1,2], Yael Lebenthal[1,2], Avivit Brener[1,2], Ravit Regev[1,2], Lars Hagenäs[3]
[1]*The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2]*The School of Medicine, Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel*
[3]*Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*

Objective: Growth assessment in achondroplasia requires disorder-specific growth charts incorporating sex- and age-specific values. Manual calculations are tedious and subject to error. We present an artificial intelligence (AI)-assisted tool that automates z-score calculations for pediatric patients with achondroplasia.

Methods: The computerized tool integrates European Lambda-Mu-Sigma (LMS) growth reference data for 9 anthropometric parameters: height, weight, body mass index, head circumference, sitting height, leg length, arm span, relative sitting height, and foot length. It inputs anthropometric measurements and transforms them into sex- and age-specific z-scores and percentiles in real time.

Results: Ten pediatric endocrinologists independently calculated anthropometric z-scores for 3 patients with achondroplasia using both the manual growth charts and the automated tool. Time-to-completion and accuracy were recorded and compared. The mean time required by the AI-assisted tool to calculate z-scores for all 9 parameters was significantly shorter than that required by manual calculation (23.4 ± 5.8 vs. 10.1 ± 2.8 minutes, p 0.001). The tool demonstrated 100% agreement with manual LMS-based calculations and eliminated human errors to which manual calculations are subject, with significantly higher median absolute z-score deviation compared to the smart tool (0.17 [0.07–0.30] vs. 0 [0–0.01], p 0.001).

Conclusions: This AI-assisted tool provides a user-friendly, accessible and highly accurate method for automated growth assessment in pediatric achondroplasia. It facilitates efficient clinical and research applications, with potential for future integration into electronic health records and web-based platforms.

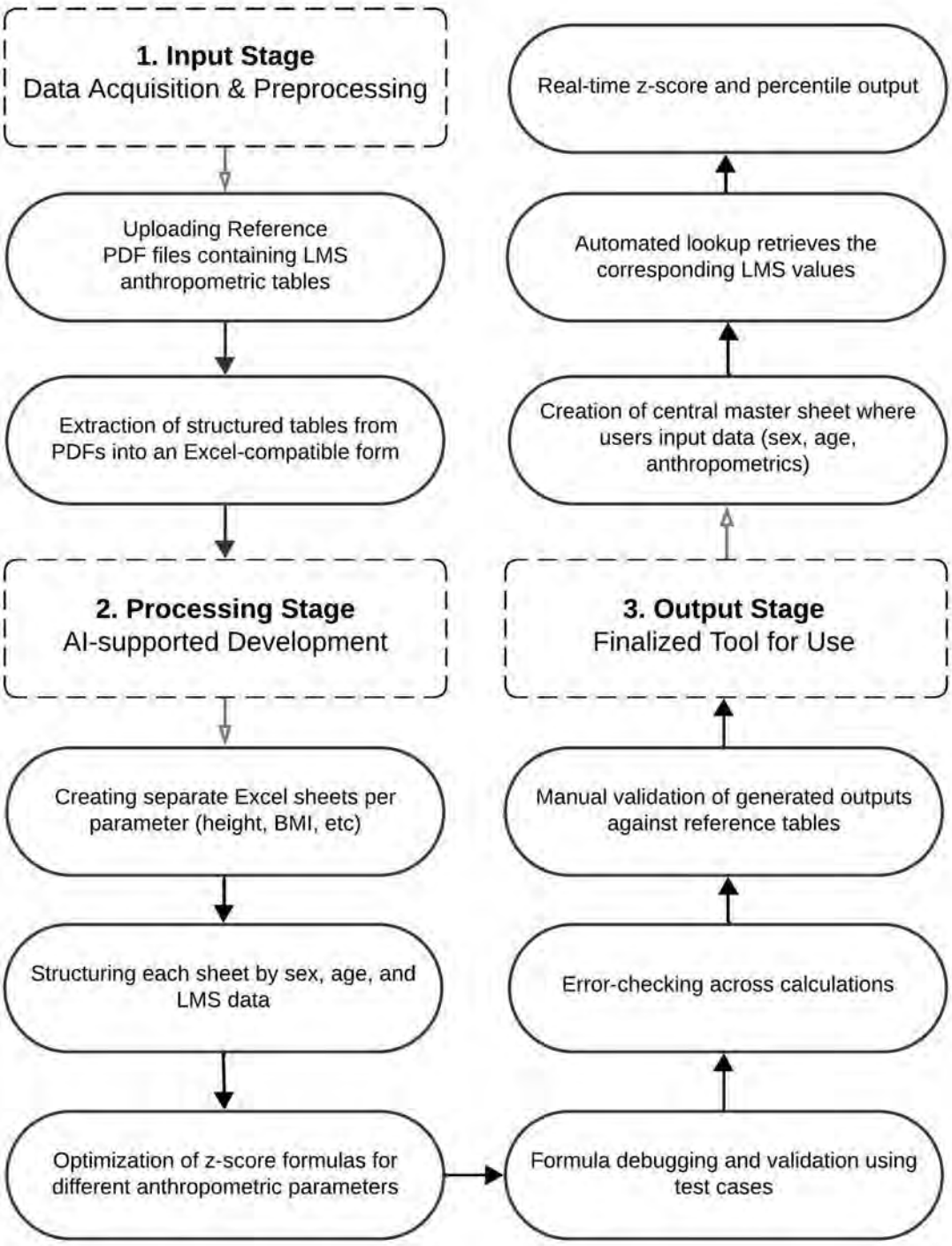

1. Input Stage
Data Acquisition & Preprocessing
Uploading Reference PDF files containing LMS anthropometric tables
Extraction of structured tables from PDFs into an Excel-compatible form
2. Processing Stage
AI-supported Development
Creating separate Excel sheets per parameter (height, BMI, etc)
Structuring each sheet by sex, age, and LMS data
Optimization of z-score formulas for different anthropometric parameters
Formula debugging and validation using test cases
Error-checking across calculations
Manual validation of generated outputs against reference tables
3. Output Stage
Finalized Tool for Use
Creation of central master sheet where users input data (sex, age, anthropometrics)
Automated lookup retrieves the corresponding LMS values
Real-time z-score and percentile output

Table 1 Median z-score deviations for anthropometric measurements across 3 cases calculated manually and using the smart AI-assisted tool

	Case 1		Case 2		Case 3		Total		
Rater	Manual	Smart	Manual	Smart	Manual	Smart	Manual	Smart	*p*
1	0.30 [0.13-0.40]	0 [0-0]	0.17 [0.12-0.36]	0 [0-0.01]	0.10 [0.05-0.11]	0 [0-0.01]	0.13 [0.09-0.33]	0 [0-0.01]	**<0.001**
2	0.20 [0.07-0.30]	0 [0-0]	0.08 [0.06-0.10]	0.01 [0-0.01]	0.15 [0.10-0.21]	0 [0-0.01]	0.10 [0.06-0.22]	0 [0-0.01]	**<0.001**
3	0.40 [0.13-0.76]	0 [0-0]	0.26 [0.17-0.56]	0 [0-0]	0.20 [0.10-0.42]	0 [0-0]	0.21 [0.16-0.54]	0 [0-0]	**<0.001**
4	0.40 [0.30-0.60]	0.04 [0.02-0.15]	0.28 [0.11-0.17]	0.02 [0-0.05]	0.12 [0.09-0.31]	0.02 [0-0.04]	0.30 [0.11-0.70]	0.03 [0-0.05]	**<0.001**
5	0.20 [0.13-0.30]	0 [0-0]	0.07 [0.06-0.26]	0 [0-0]	0.10 [0.05-0.21]	0 [0-0]	0.13 [0.07-0.27]	0 [0-0]	**<0.001**
6	0.24 [0.13-0.3]	0.02 [0-0.04]	0.17 [0.06-0.26]	0.03 [0.01-0.03]	0.11 [0.05-0.16]	0.01 [0-0.02]	0.17 [0.08-0.25]	0.02 [0-0.03]	**<0.001**
7	0.30 [0.30-0.50]	0 [0-0.01]	0.17 [0.06-0.30]	0 [0-0.02]	0.10 [0.05-0.21]	0 [0-0.01]	0.22 [0.10-0.31]	0 [0-0.01]	**<0.001**
8	0.30 [0.20-0.38]	0 [0-0]	0.07 [0.04-0.11]	0.01 [0-0.03]	0.05 [0.01-0.11]	0.01 [0.01-0.02]	0.11[0.04-0.24]	0 [0-0.02]	**<0.001**
9	0.32 [0.18-0.40]	0 [0-0.01]	0.16 [0.10-0.21]	0.01 [0-0.03]	0.05 [0-0.07]	0.01 [0-0.02]	0.16 [0.06-0.22]	0 [0-0.03]	**<0.001**
10	0.22 [0.20-0.30]	0 [0-0]	0.17 [0.07-0.21]	0 [0-0.01]	0.1 [0.05-0.20]	0 [0-0]	0.20 [0.10-0.23]	0 [0-0]	**<0.001**
	Case 1			Case 2			Case 3			**Total**		
All	Manual	Smart	*p*	Manual	Smart	*p*	Manual	Smart	*p*	Manual	Smart	*p*
	0.30 [0.15-0.40]	0 [0-0.01]	**<0.001**	0.17 [0.07-0.30]	0 [0-0.03]	**<0.001**	0.10 [0.05-0.21]	0 [0-0.01]	**<0.001**	0.17 [0.07-0.30]	0 [0-0.01]	**<0.001**

The data are expressed as median [interquartile range bounds]. Values reflect the median absolute z-score deviation from the gold-standard reference, defined as the output of the AI-assisted tool when used by the tool's developer. The column labeled 'total' summarizes deviations across all 3 cases per evaluator. The row labeled "all" summarizes deviations across all evaluators. **Bold** indicates statistical significance at a $p = 0.05$ level (Mann-Whitney-Wilcoxon test).

116

Second Primary Malignancies among Pediatric and Young Adult Survivors of Differentiated Thyroid Cancer: Real-World Evidence

Rachel Bello Vitrial[1], Michal Yackobovitch-Gavan[1,2], Liora Lazar[1,3], Samah Hayek[2]
[1]*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*
[2]*Deptartment of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

Background:

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy among children, adolescents, and young adults (CAYA). While prognosis is generally favorable, rising incidence, longer survivorship, and radioiodine (RAI) treatment raise concern for late effects, particularly second primary malignancies (SPMs).

Objective:

To assess SPM risk and impact of RIA among CAYA DTC survivors.

Methods:

Retrospective cohort study (1982–2022) using Clalit Health Services records, including DTC patients diagnosed 40 years, who survived ≥2 years. Participants were matched to cancer-free controls (1:4) by birth year, sex, ethnicity, and socioeconomic status. Cox models estimated hazard ratios (HRs) with 95% confidence intervals (CIs).

Results:

Among 5,267 DTC survivors (10% diagnosed before age 20) and 21,062 matched controls, SPM incidence was higher in survivors with 50% increased risk (500 vs. 360 per 100,000 person-years; HR 1.50, 95% CI 1.34–1.67) and occurred after a shorter latency (13.8 vs. 15.1 years; P=0.042). Survivors diagnosed before age 20 were significantly younger at data retrieval than those diagnosed at 20–40 years (median 33 vs. 47 years; P0.001) and had significantly lower SPM rates (5.6% vs. 9.0%; P=0.012). In DTC survivors SPM risk increased with cumulative RAI exposure (for 0, 1, and ≥2 doses, HR 1.20, 1.91, and 2.73, respectively; P0.001). Overall mortality rate was low (3.3%) and similar to that of matched controls but was significantly higher among survivors who developed SPMs and/or received RAI treatment (P0.001).

Conclusions:

Over four decades of follow-up, SPMs were identified as a significant long-term risk among CAYA DTC survivors, frequently manifesting many years after the initial diagnosis. Both SPM occurrence and higher cumulative RAI doses were associated with increased mortality. These findings underscore the need for extended surveillance, particularly for those diagnosed in childhood or adolescence, as malignancies may arise many years after diagnosis.

117

Comparison of pre-treatment glycemic control in women undergoing assisted reproductive technology resulting in live birth and those that did not

Shani Erez[1,2], Tal Schiller[1,3], Alena Kirzhner[1,3], Yuval Or[1,4]
[1]*The Hebrew University–Hadassah School of Medicine, Jerusalem, Israel*
[2]*Department of Military Medicine and Tzameret, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*
[3]*Department of Diabetes, Endocrinology and Metabolism, Kaplan Medical Center, and Faculty of Medicine, Hebrew University of Jerusalem, Rehovot, Israel*
[4]*5Department of Obstetrics and Gynecology, Kaplan Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Rehovot, Israel*

Background: Diabetes and prediabetes are increasingly prevalent in women of reproductive age and may affect fertility outcomes. Data regarding the impact of pre-treatment glycemic control on assisted reproductive technology (ART) live birth rates are limited.

Objective: To examine whether glycemic control, assessed by HbA1C and fasting plasma glucose levels before ART, differs between women whose treatment resulted in live birth and those whose treatment did not.

Methods: This retrospective case–control study included women with pregestational diabetes or prediabetes treated at Kaplan Medical Center, Rehovot, between January 2014 and April 2024. Clinical and demographic data, laboratory results, and ART outcomes were collected. The primary outcome was the comparison of glycemic control between live birth and non-live birth groups. Secondary outcomes included obstetric and neonatal complications.

Results: 17 women undergoing a total of 44 ART cycles met the inclusion criteria. Live birth occurred in 17 cycles (38.6%). Fasting glucose prior to treatment was significantly higher in the live birth group compared to the no live birth group (115 ± 14.3 vs. 102.19 ± 15.08 mg/dL, p = 0.008). HbA1C levels did not differ significantly (6.28 ± 0.65 vs. 6.08 ± 0.45, p = 0.244). Obstetric complications among live birth pregnancies included preterm birth (23.53%), large-for-gestational-age infants (41.18%), and high cesarean delivery rate (76.47%).

Conclusions: Fasting glucose, but not HbA1C, was associated with ART live birth outcomes in women with diabetes and prediabetes. The high complication rates highlight the importance of close monitoring and tailored management in this population.

Obesity, Pregnancy, reproduction and fertility, Type 2 diabetes and glucose regulation

Polycystic Ovary Syndrome and Gestational Dysglycemia: A Large Population-Based Cohort Study

Yulia Balmakov[1,2], Orit Pinhas-Hamiel[3,4], Hertzel C Gerstein[5], Gabriel Chodick[6], Maya Nitecki[1,7], Estela Derazne[4], Yael Barer[6], Noah Gruber[8,9], Aya Bardugo[1,2], Cole D. Bendor[1,2], Avi Shina[2], Arnon Afek[10,11], Tali Cukierman-Yaffe[6,12], Adi Vinograd[13,14], Gilad Twig[6,12]

[1]*Department of Military Medicine, Faculty of Medicine, Hebrew University Jerusalem, Israel.*

[2]*Israel Defense Forces, Medical Corps, Ramat Gan, Israel.*

[3]*Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel.*

[4]*School of Medicine, Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel.*

[5]*Department of Medicine, McMaster University, Hamilton, Ontario, Canada.*

[6]*Department of Preventive Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Israel.*

[7]*Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, NC, USA.*

[8]*Faculty of Medical and Health Science, Tel Aviv University, Tel Aviv, Israel.*

[9]*Pediatric Endocrinology and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer, Israel.*

[10]*The Dina Recanati School of Medicine, Reichman University, Herzliya, Israel.*

[11]*Central Management, Sheba Medical Center, Ramat Gan, Israel The Dina Recanati School of Medicine, Reichman University, Herzliya, Israel.*

[12]*Division of Endocrinology Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel.*

[13]*The Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel.*

[14]*Department of Epidemiology and Preventive Medicine, School of Public Health, Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel.*

Background: Polycystic ovary syndrome has been linked to an increased risk of gestational diabetes mellitus, but its association with the full spectrum of gestational dysglycemia is unknown.

Objective: To evaluate the association between polycystic ovary syndrome and the full spectrum of gestational dysglycemia, including abnormalities below the gestational diabetes threshold, in a large, universally screened population.

Study Design: In this retrospective cohort study, we included women who underwent a mandatory military pre-recruitment medical evaluation (ages 16–19) and who, between 2001 and 2019, also completed a two-step gestational diabetes screening, during their first pregnancy, in the second-largest healthcare provider in Israel. Women were categorized into four groups: gestational normoglycemia, abnormal glucose challenge test with a normal oral glucose tolerance test, gestational impaired glucose tolerance, and gestational diabetes mellitus. Multivariable logistic regression models and sensitivity analyses were applied for evaluating gestational dysglycemia in women with versus without PCOS.

Results: Among 177,241 women, 13,648 (7.7%) had a diagnosis of polycystic ovary syndrome. Among women with polycystic ovary syndrome, 9.1% had an abnormal glucose challenge test with a normal oral glucose tolerance test, 4.9% had gestational impaired glucose tolerance, and 6.3% were diagnosed with gestational diabetes mellitus. The respective adjusted odds ratios (ORs) associated with PCOS were 1.18 (95% CI 1.11-1.26), 1.26 (1.16-1.37), 1.61 (1.49-1.73), and 1.31 (1.25-1.37). Results remained consistent following adjustment for pre-pregnancy body mass index. Women with polycystic ovary syndrome and high body mass index at adolescence demonstrated an odd ratio of 2.69 (2.30–3.14) for any dysglycemia.

Conclusion: Women with polycystic ovary syndrome, and particularly those with concomitantly high body mass index, constitute a high-risk subgroup for gestational dysglycemia below the gestational diabetes mellitus threshold, suggesting the importance of pre-pregnancy mitigation of modifiable risk factors, given its potential maternal and perinatal implications.

Key Words: Body mass index, Gestational diabetes mellitus, Gestational dysglycemia spectrum, Non-GDM range, Polycystic ovary syndrome, Pregnancy.

119

Beta cells intrinsically sense and limit their secretory activity via mTORC1-RhoA signaling

Saar Krell[1], Aharon Helman[1]
The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem

Pancreatic β cell activity is precisely regulated to prevent hypoglycemia induced by excessive insulin release. Theoretical considerations and empirical evidence suggest that glucose-stimulated insulin secretion is self-limited, resulting in biphasic and oscillatory patterns of secretion to maintain balanced blood insulin and glucose levels.
However, the molecular underpinnings of an intrinsic feedback mechanism, including how β cells sense their extent of secretion and how they limit it, remain elusive. Here, we identify mTORC1 as a critical sensor and negative regulator of insulin secretion.
Under physiological conditions, mTORC1 activation in β cells occurs rapidly in response to glucose stimulation and depends on glucose metabolism, closure of ATP- sensitive potassium channels, and Ca 2+ influx. Transient mTORC1 inhibition during glucose stimulation enhances insulin secretion, indicating that it may act as a feedback inhibitor of the pathway. Mechanistically, mTORC1 activation following glucose stimulation modulates the phosphorylation of proteins governing actin remodeling and vesicle trafficking, particularly the RhoA-GTPase pathway. Acute mTORC1 inhibition during glucose stimulation reduces RhoA activation and F-actin polymerization, thereby increasing the second phase of insulin secretion, which is controlled by vesicle trafficking. Restoring RhoA activity normalizes actin polymerization and insulin release despite mTORC1 inhibition, indicating that RhoA is a downstream effector of the mTORC1-mediated response to glucose in β cells. We propose that the glucose-mTORC1-RhoA axis, through F-actin remodeling, forms an autonomous feedback mechanism that limits insulin exocytosis, and may contribute to prevention of hypoglycemia.

Population-Based Age-Specific Reference Percentiles and Z-Scores for AMH in Women

Rina Hemi[1], Ronit Machtinger[2,3], Ehud Barhod[1], Tomer Ziv[3,4]
[1]*Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel, Endocrine Laboratory*
[2]*Department of Obstetrics and Gynecology, Sheba Medical Center, Ramat Gan, Israel, IVF Division*
[3]*Tel Aviv University, Tel Aviv, Israel, Gray Faculty of Medical & Health Sciences*
[4]*Tel Aviv University, Tel Aviv, Israel, Baran Department of Epidemiology and Preventive Medicine, School of Public Health*

Anti-Müllerian hormone (AMH) is a reliable biomarker for assessing ovarian reserve, offering insight into the quantity of a woman`s remaining oocyte pool. As AMH levels naturally decline with age, establishing accurate reference values is crucial for fertility assessment and reproductive planning. While existing nomograms predominantly focus on infertile populations or small cohorts, the current study presents a comprehensive, population-based analysis of AMH levels in 5,230 women aged 25 to under 45 years. Serum samples were obtained through a central laboratory in a large tertiary hospital (Sheba Medical Center) which processes AMH tests collected primarily in the community. This unique setting provides a broadly representative sample of women from a community-based population. Utilizing these community-based serum samples measured using the Elecsys Cobas AMH assay; this cross-sectional study developed age-specific AMH percentiles and z-scores using the general additive model for location, scale, and shape (GAMLSS).

Participants were randomly split into a learning group (n=4,000) and a validation group (n=1,230), with similar median age (34.3 vs. 34.2 years, p=0.499) and AMH (1.83 vs. 1.85 ng/mL, p=0.584) levels. Median AMH values demonstrated a clear age-dependent decline, ranging from 3.03 ng/mL at age 25 to 0.31 ng/mL at age 44. The generated reference chart enables interpretation of AMH results in relation to age-matched peers, enhancing the clinical utility of AMH testing for counseling and decision-making in both individual and public health contexts.

Importantly, this study addresses a gap in current literature by including a community-based population and avoiding the selection biases inherent in studies limited to women with infertility or polycystic ovary syndrome. The mean z-score in the validation group was approximately zero, confirming the model’s robustness.

These results reinforce the value of AMH as a tool for fertility assessment, while highlighting variability in AMH across populations and emphasizing the need for standardized reference ranges. The newly established percentiles may support timely fertility preservation decisions and inform public health strategies aimed at fertility awareness in reproductive-aged women. As AMH testing becomes increasingly accessible, age-specific interpretation using robust population data will become essential in tailoring personalized reproductive care.

121

The risk of type 2 diabetes in women with normal glucose challenge test in pregnancy; Implications for diabetes screening and prevention strategy

Yael Barer[1,2], Tal Schiller[2,3], Maya Nitecki[1,4], Gilad Twig[1,5], Gabriel Chodick[1]
[1]*Department of Preventive Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University*
[2]*Maccabi Healthcare Services*
[3]*Institute of Endocrinology, Diabetes and Metabolic Disease, Wolfson Medical Center*
[4]*Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, NC, USA*
[5]*Division of Endocrinology Diabetes and Metabolism, Sheba Medical Center*

Aims

The rising obesity pandemic among young adults has coincided with increasing rates of T2DM, creating an urgent clinical need for improved detection and prevention strategies. To better identify women at high risk, we aim to investigate the association between pregnancy glucose challenge test (GCT) results within the normal range and the risk of subsequent type 2 diabetes mellitus (T2DM), overall and across pre-pregnancy BMI categories.

Materials and methods

This retrospective cohort study identified women aged 20-50 years who underwent GCT screening for gestational diabetes between 2004-2022, had normal GCT results (140mg/dL), and no prior diabetes. Follow-up for T2DM extended from date of last GCT until 31 September 2024.

Results

Among 243,819 eligible women (mean age 32.7 years), 1,255 developed T2DM during a median follow-up of 6.8 years. The cumulative risk of T2DM in women with normal pre-pregnancy BMI and GCT of 70-89 mg/dL was 0.22 per 10,000 person-years. Compared to this reference group, women with a GCT of 130–140 mg/dL had adjusted Hazard Ratio (HR) for T2DM ranging from 15.3 (95% confidence interval [CI] 6.7-34.7) among women with normal BMI, 42.4 (95% CI 19.9, 90.5) among women with overweight, to 171 (95% CI 79.8-366) among women with obesity.

Conclusions

While most women with normal GCT and normal pre-pregnancy BMI have a very low risk of subsequent T2DM, those with pre-pregnancy overweight or obesity have a substantially elevated risk. These results may have important implications in prioritizing screening for T2DM in mid-adulthood.

122

A Pilot Randomized Controlled Trial of Low-versus Standard-Carbohydrate Diets in Women with Gestational Diabetes Mellitus: Effects on Maternal Ketone Levels, Glycemic Control, and Obstetric Outcomes

kim Goldberg-Politzer[1], Assaf Buch[2,3], Tomer Avnon[4,5], Shiraz Vered[6], Roni Elran-Barak[1], Daniela Saunyama[2,3], Roy Eldor[3,4], Yariv Yogev[4,5], **Marianna Yaron**[3,4]

[1]*School of Public Health, University of Haifa, Haifa, Israe*

[2]*Department of Nutritional Sciences, School of Health Sciences, Ariel University, Ariel, Israel*

[3]*Institute of Endocrinology, Diabetes, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

[4]*Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

[5]*Lis Hospital for Women's Health, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

[6]*Department of Statistics, University of Haifa, Haifa, Israel*

Objectives: To evaluate the feasibility, short-term safety, and early metabolic and perinatal effects of a supervised moderately low-carbohydrate diet (~120 g/day) compared with the standard recommended 175 g/day diet among pregnant women with gestational diabetes mellitus (GDM).

Methods: This single-center, open-label pilot randomized controlled trial enrolled 20 women with GDM at 24–28 weeks' gestation, who were randomized 1:1 to either a standard-carbohydrate diet (NCD, 175 g/day) or a moderately low-carbohydrate diet (LCD, ~120 g/day). Both groups received Mediterranean-style medical nutrition therapy and bi-weekly follow-up with a dietitian until delivery. The primary outcome was maternal capillary ketone (β-hydroxybutyrate) concentration at study visits. Secondary outcomes included self-monitored blood glucose (SMBG) profiles, need for pharmacologic therapy, gestational weight gain, fetal biometry, and obstetric and neonatal outcomes.

Results: Median blood ketone (β-hydroxybutyrate) concentrations were modest in both groups and slightly higher with LCD (0.25 vs 0.16 mmol/L; P=0.029), all remined substantially below the upper physiological threshold, with no ketone-associated adverse events. Carbohydrate intake differed significantly (LCD 119 g/day vs NCD 168 g/day; P0.001), and adherence was high. Rates of initiation of pharmacologic therapy were similar (36% LCD vs 44% NCD). Fasting and postprandial glucose levels were comparable, with directionally lower values in the LCD group. There were no differences in the maternal of neonatal composite outcomes between the groups. Four non-serious adverse events occurred in the LCD group.

Conclusion: A supervised moderately low-carbohydrate diet (~120 g/day) appears feasible, acceptable, and safe for women with GDM, maintaining blood ketone levels within physiological ranges and showing favorable trends in maternal glycemia and fetal growth. These findings support evaluation in larger trials.

Long-term health issues related to differences in sex development

Orit Futterman[1,2], Amit Eben Chaime[1,2], Moshe Phillip[1,2], David Ben Meir[2,3], **Liat de Vries**[1,2]

[1]*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel*

[2]*Faculty of Medical & Health Sciences, Tel Aviv University*

[3]*Pediatric Urology Unit, Schneider Children's Medical Center of Israel*

Background: Differences in sex development (DSD) comprise a heterogeneous group of conditions that require complex, lifelong management. Owing to their multifaceted nature, continuous follow-up and a holistic, multidisciplinary approach are essential. However, data regarding long-term health outcomes beyond childhood remain limited.

Objective: To assess general health status, metabolic outcomes, and therapeutic management in individuals with DSD followed at a tertiary pediatric center.

Methods: Clinical data were retrospectively collected from medical records and included demographic characteristics, medical history, medication records, anthropometric measurements, and laboratory findings.

Results: A total of 109 individuals with DSD (82.6% male) were evaluated over a median follow-up period of 16 years (range 6–35 years). The cohort included 73 patients with 46,XY DSD (66.9%), 15 with 46,XX DSD (13.7%), and 11 with sex chromosome DSD (9.2%). Karyotype data were unavailable for 10 patients (9.2%), including 3 who were referred but did not complete the recommended evaluation and 7 who were not referred for testing. Neuropsychiatric morbidity was identified in 20.2% of patients, acne before age 20 in 18.3%, dyslipidemia in 11%, and osteoporosis in 4.6%. Attention-deficit/hyperactivity disorder was the most prevalent psychiatric diagnosis, followed by anxiety disorders, autism spectrum disorder, developmental delay, depression, and obsessive–compulsive disorder. Chromosomal karyotype was significantly associated with the presence of dyslipidemia. Sixteen patients (14.6%) were lost to follow-up, and five (4.5%) continued hormone replacement therapy under primary care without structured specialist supervision.

Conclusions: DSD constitutes a chronic condition with significant long-term physical and mental health consequences, underscoring the need for lifelong, multidisciplinary care. The early emergence of morbidity reinforces this requirement. The loss of follow-up in approximately one-fifth of patients highlights the critical importance of structured and accessible transition to adult care services. Increased awareness is also needed to ensure completion of karyotyping and etiological evaluation in patients diagnosed in childhood with incomplete diagnostic assessment.

125

Mitotic Count and Ki-67 Index in Gastroenteropancreatic Neuroendocrine Neoplasms: Concordance Analysis and Association With Metastatic Disease.

Mohammad Sheikh Ahmad[1,2], Abed Agbarya[2,3], Sharon Talisman[1,2], Jacob Bejar[4], Hila Kreizman Shefer[4], Monica Laniado[2,5], Leonard Saiegh[1,2]

[1]*Institute of Endocrinology, Bnai Zion Medical Center, Haifa, Israel*

[2]*The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel*

[3]*Institute of Oncology, Bnai Zion Medical Center, Haifa, Israel*

[4]*Institute of Pathology, Bnai Zion Medical Center, Haifa, Israel*

[5]*Department of Surgery, Bnai Zion Medical Center, Haifa, Israel*

Background: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are graded per the World Health Organization (WHO) using mitotic count and Ki-67 index. There is ongoing debate regarding the concordance between these parameters and their ability to predict metastatic disease.

Objective: To assess concordance between mitotic count and Ki-67 index in grading GEP-NENs and to determine which parameter more accurately relates to metastatic disease and local tumor behavior.

Methods: We conducted a single-center retrospective cohort study of adults with GEP-NENs managed between January 2006 and February 2024. Tumors were staged according to the TNM system. Grading followed WHO criteria using mitotic count and Ki-67 index; when discordant, the higher grade was assigned.

Results: Concordance between mitotic count- and Ki-67-based grading was 76.5% (78/102) with Cohen's κ=0.36, indicating fair-to-moderate agreement. More tumors were classified as G1 by mitotic count (86.3%) than by Ki-67 index (68.6%). Neither mitotic count nor Ki-67 index (numerical values or grades) showed a significant association with metastatic disease (all p0.05). Mitotic count (as a numerical continuous values) correlated with tumor invasion (T1 vs T3, p=0.035; T1 vs T4, p=0.036), whereas Ki-67 index did not (p=0.11). Tumor size was the strongest predictor of metastases (lymph-node p=0.028; distant p0.001; any p0.001).

Conclusions: Mitotic count and Ki-67 index show only 76.5% concordance. Neither marker predicted metastatic disease in this cohort, while tumor size was the most robust predictor. These findings support giving greater weight to tumor size within prognostic algorithms, while recognizing the limitations of proliferation-based grading for predicting metastasis.

126

Predictive Value of Morning Serum Cortisol for Synacthen Test Outcomes During Corticosteroid Withdrawal

Leonard Saiegh[1,2], Balsam Dakwar[1], Katya Jovanovic[1], Muaweya Mahamed[3], Hadas Rabani[1], Anan Shalata[1], Emad Khoury[1], Mohammad Sheikh Ahmad[1,2]

[1]*Institute of Endocrinology, Bnai Zion Medical Center, Haifa, Israel*

[2]*The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel*

[3]*Department of internal medicine B, Bnai Zion Medical Center, Haifa, Israel*

Background: Prolonged corticosteroid therapy may result in hypothalamic–pituitary–adrenal axis suppression and subsequent adrenal insufficiency. The short Synacthen stimulation test remains the gold standard for assessing adrenal function, yet morning serum cortisol may serve as a valuable screening tool during corticosteroid withdrawal.

Objective: To evaluate the diagnostic performance of morning serum cortisol in predicting Synacthen stimulation test outcomes during glucocorticoid withdrawal and to compare the results of high-dose versus low-dose Synacthen stimulation protocols.

Methods: This retrospective analysis examined 164 Synacthen stimulation tests performed between 2006–2021 in patients undergoing prednisone withdrawal assessment. Low-dose Synacthen stimulation testing (1 µg Synacthen) was utilized from 2006–2010, followed by high-dose Synacthen stimulation testing (250 µg Synacthen) from 2010–2021. Receiver operating characteristic analysis was employed to determine optimal morning serum cortisol thresholds for predicting adequate adrenal response, defined as cortisol ≥18 µg/dL (500 nmol/L) at 30 minutes.

Results: No significant differences were observed between low-dose and high-dose Synacthen stimulation protocols regarding stimulated cortisol levels or test outcomes. Receiver operating characteristic analysis revealed optimal morning serum cortisol thresholds of 10.4 µg/dL (287 nmol/L) for low-dose testing and 11.2 µg/dL (309 nmol/L) for high-dose testing. In the entire cohort, a morning serum cortisol threshold of 10.9 µg/dL (301 nmol/L) demonstrated balanced sensitivity (70%) and specificity (85.5%). Notably, among patients with morning serum cortisol levels between 10–15 µg/dL (276–414 nmol/L), and 10–12 µg/dL (276–331 nmol/L), 40% and 48% failed the Synacthen stimulation test, respectively.

Conclusions: No significant differences were observed between low-dose and high-dose Synacthen stimulation protocols regarding stimulated cortisol levels or test outcomes, and morning serum cortisol provides valuable adjunctive information for assessing hypothalamic–pituitary–adrenal axis recovery. However, a substantial proportion of patients with morning serum cortisol near the recommended discontinuation threshold of 10 µg/dL (300 nmol/L) still demonstrate abnormal Synacthen stimulation test responses.

127

Clinical characteristics and outcomes of thyrotoxicosis in amiodarone-treated individuals with prior hypothyroidism

Afif Nakhleh[1,2], Limor Adler[3,4], Shirley Shapiro Ben David[3,4], Daniella Rahamim-Cohen[3], Ori Liran[3,4], Sagit Zolotov[1,2]

[1]*Diabetes and Endocrinology Clinic, Maccabi Healthcare Services, Haifa, Israel*

[2]*Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus, Haifa, Israel*

[3]*Health Division, Maccabi Healthcare Services, Tel Aviv, Israel*

[4]*Faculty of Medicine, Tel Aviv University, Israel*

Background and Aims: Evidence regarding the transition from hypothyroidism to thyrotoxicosis in amiodarone-treated patients remains scarce. This study compared clinical characteristics, treatments, and outcomes in amiodarone-exposed individuals who developed thyrotoxicosis following hypothyroidism versus those without prior thyroid disease.

Methods: This retrospective cohort study utilized electronic health records from Maccabi Healthcare Services, an Israeli health maintenance organization. We included adults from the cardiovascular disease registry with new-onset thyrotoxicosis diagnosed between January 1, 2010, and December 31, 2022, who received amiodarone within the year preceding diagnosis. Eligibility required two consecutive TSH measurements 3 months apart) in the preceding 10 years or levothyroxine dispensation in the preceding year. Follow-up ended on August 31, 2025. Data were analyzed using chi-square or Fisher's exact tests, t-tests or Mann-Whitney U tests, and Cox regression models adjusted for age and sex.

Results: We included 558 adults with new-onset thyrotoxicosis who were receiving active amiodarone treatment or had discontinued it within the preceding year. Of these, 467 had no prior thyroid disease (T-controls) and 91 had prior hypothyroidism (post-hypo-T). Compared with T-controls, post-hypo-T individuals were older (70.4±10.1 vs. 67.4±11.0 years; P=0.02), had a higher proportion of males (44.0% vs. 25.3%; P 0.001) and had slightly shorter median amiodarone exposure (2.7 [interquartile range (IQR), 1.5–4.3] vs. 2.8 [IQR, 1.6–3.2] years; P=0.01). At diagnosis, post-hypo-T individuals had lower median free thyroxine (fT4) levels (27.0 [IQR, 22.8–32.8] vs. 31.3 [IQR, 20.5–45.2] pmol/L; P 0.001) and free triiodothyronine (fT3) levels (6.4 [IQR, 5.3–8.2] vs. 7.5 [IQR, 5.7–10.8] pmol/L; P 0.001).

Over a median follow-up of 7.8 [IQR, 5.2–11.5] years, antithyroid medications were used less frequently in post-hypo-T individuals (37.4% vs. 54.0%; adjusted hazard ratio [aHR] 0.59; P=0.004). Glucocorticoid use was lower in post-hypo-T individuals (26.4% vs. 38.5%; aHR 0.67; P=0.06), though this difference did not reach statistical significance. Post-hypo-T individuals had a higher incidence of hypothyroidism requiring levothyroxine (64.8% vs. 17.8%; aHR 6.12; P 0.001).

Conclusions: Current or recent amiodarone users with post-hypo-T present with milder thyrotoxicosis and more often revert to hypothyroidism requiring levothyroxine. This distinct clinical entity (representing 16% of cases and likely driven by destructive thyroiditis) demonstrates that a history of hypothyroidism does not eliminate the risk of thyrotoxicosis, mandating continued clinical vigilance.

130

DXA screening in men aged ≥70 years: high burden of low bone density and favorable health-economic profile in a real-world Israeli cohort

Vanessa Rouach[1,2], Ziv Versano[3], Meital Sasson[3], Yona Greenman[4], Arnon Makori[3], Inbal Goldshtein[5]

[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel*

[2]*The Dr. Miriam and Sheldon G. Adelson School of Medicine (The Gray School), Tel Aviv University, Israel*

[3]*Assuta Medical Centers*

[4]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center*

[5]*KI Research Institute*

Background

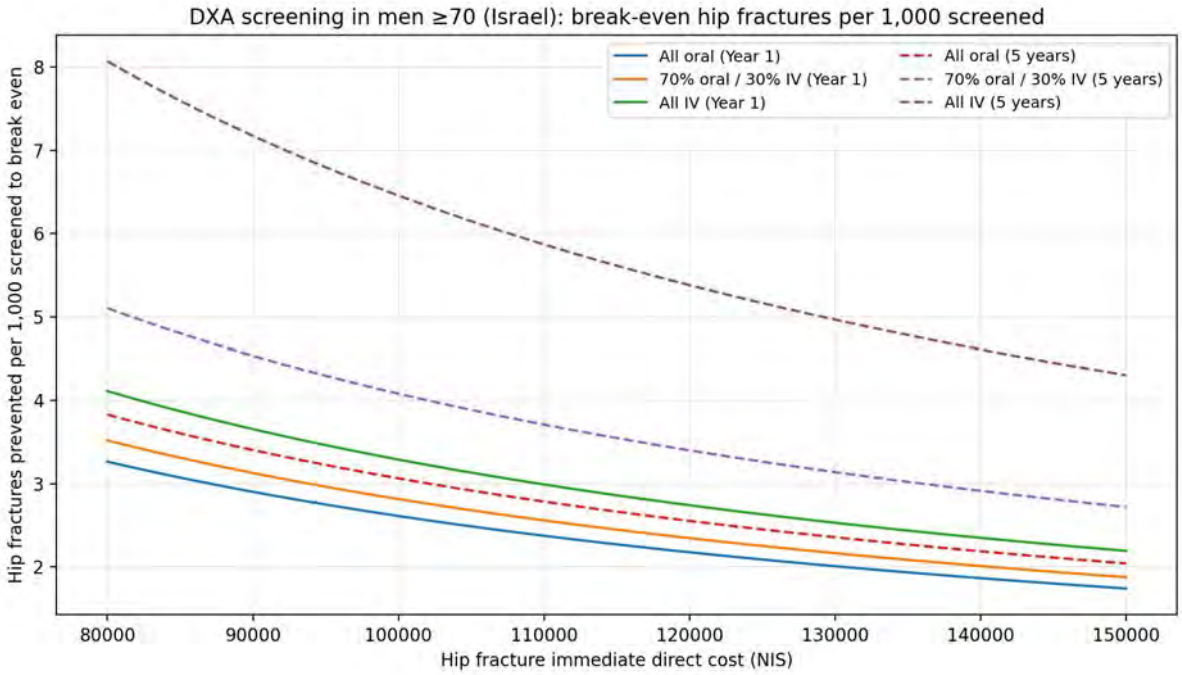
Osteoporosis in men remains underdiagnosed despite high fracture-related morbidity and mortality. While dual-energy X-ray absorptiometry (DXA) is the gold standard for bone mineral density (BMD) assessment, routine screening in men remains controversial due to inconsistent guideline recommendations. In Israel, Maccabi Healthcare Services implemented a targeted DXA screening policy for men aged ≥70 years in 2012. We assessed the burden of low BMD in men undergoing DXA and evaluated the health-economic implications of age-targeted screening.

Methods

We conducted a retrospective analysis of DXA examinations performed in men at Assuta Medical Centers between 2014 and 2024 using the MDClone platform. Men aged ≥18 years were included, with a predefined screening subgroup of men aged ≥70 undergoing their first DXA. Demographic data, body mass index (BMI), smoking status, diabetes, and fracture history were extracted. BMD was classified as normal, osteopenia, or osteoporosis by T-score. A budget-impact and break-even analysis was performed using Israeli unit costs. Model inputs included DXA cost, osteoporosis prevalence from the cohort, published Israeli hip fracture costs, and fracture risk reduction with anti-osteoporotic therapy.

Results

More than 86,000 DXA examinations in men were analyzed. Overall, 9,728 men (11.3%) had osteoporosis, 33,408 (38.8%) osteopenia, and 43,578 (50.0%) normal BMD. Median age was approximately 71 years, with the largest group aged 70–75 years. Median BMI increased across osteoporosis (25.3 kg/m²), osteopenia (26.6 kg/m²), and normal BMD (27.5 kg/m²). Smoking prevalence ranged from 9.5% to 11.7% and diabetes from 6.3% to 9.9%, while reported fracture prevalence at referral was low. Per 1,000 men screened, DXA identified ~113 men eligible for therapy. Program costs were approximately 260,000–330,000 NIS in the first year, with break-even achieved if only 2.6–3.3 hip fractures were prevented in the first year or 3–6 over five years.



Conclusion

Men aged ≥70 undergoing DXA in Israel have a high prevalence of clinically actionable low BMD. Using Israeli cost structures, preventing only a small number of hip fractures per 1,000 screened would fully offset screening and treatment costs. These real-world data support age-targeted DXA screening in older men as both a clinically high-yield and economically efficient public-health strategy.

131

Evaluation of bone health after cancer diagnosis: Gaps in DXA assessment and implications for clinical care

Vanessa Rouach[1,2], Ziv Versano[3], Meital Sasson[3], Yona Greenman[1], Arnon Makori[3]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel*
[2]*School of Medicine, Faculty of Medical and Health Sciences*
[3]*Assuta Medical Centers*

Background:
Cancer-induced bone loss (CIBL) is a frequent but under-recognized complication of malignancy and its treatments. Early assessment of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA) is recommended to identify patients at increased fracture risk; however, real-world utilization and timing of DXA after cancer diagnosis remain poorly characterized.

Objectives:
To evaluate DXA utilization, timing of assessment, BMD and T-score results, and the prevalence of osteopenia and osteoporosis following a new cancer diagnosis in a large real-world cohort.

Methods:
We conducted a retrospective cohort study using the MDClone platform to identify adults with a first cancer diagnosis between 01 January 2015 and 31 December 2024 at Assuta Medical Centers. Demographic characteristics, smoking status, DXA performance and timing, BMD values, and T-scores were extracted. Bone status was classified according to World Health Organization criteria using the lowest T-score across all measured DXA sites (lumbar spine, femoral neck, or total hip).

Results:
Among 21,112 patients with newly diagnosed cancer (77.0% women), 7,644 (36.2%) underwent DXA assessment at any time following diagnosis. DXA utilization was substantially lower in men than in women (15.5% vs. 42.5%). Early DXA assessment within 6 months of diagnosis was uncommon, occurring in only 1,578 patients (7.5%). DXA utilization varied by cancer type, with the highest rates observed in breast and prostate cancers.
Among patients who underwent DXA, 34.4% had normal BMD, 48.5% were classified as having osteopenia, and 17.1% met criteria for osteoporosis. Mean BMD and T-scores among DXA performers were 0.86 ± 0.15 g/cm² and -1.02 ± 1.21 at the femoral neck, 0.87 ± 0.26 g/cm² and -0.67 ± 1.19 at the total hip, and 1.00 ± 0.61 g/cm² and -0.53 ± 1.55 at the lumbar spine, respectively.

Conclusions:
In this large real-world oncology cohort, DXA assessment after cancer diagnosis was markedly underutilized and frequently delayed, with pronounced disparities by sex. Despite low screening rates, nearly two-thirds of patients who underwent DXA had abnormal bone density, and more than one in six met criteria for osteoporosis. These findings highlight a substantial burden of unrecognized skeletal disease and underscore the need for systematic integration of bone health assessment into routine oncologic care.

132

Impact of ethnicity and antihyperglycemic medications on dementia incidence in older adults with type 2 Diabetes

Elena Chertok Shacham[1,2], Sireen Sharif[3], Muhammad Kadeh[4], Snait Ayalon[3]
[1]*Endicrinology, Emek medical center*
[2]*Medical, Technion, Israel Institute of technology*
[3]*Research authority, Emek medical center*
[4]*internal medicine department B, Emek medical center*

Background

Type 2 diabetes increases the risk of cognitive decline and dementia. Data on ethnic differences in dementia prevalence among patients with diabetes remain limited.

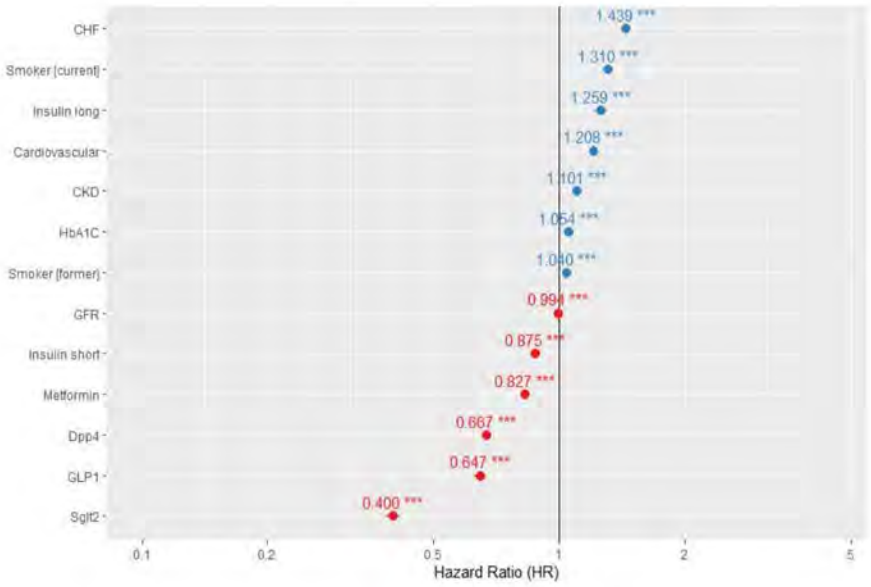
Methods:

We conducted a retrospective matched case–control study of Clalit Health Services members aged 60 or older. Matching (1:3) was based on age, sex, language, and socioeconomic status. Ethnicity was determined by spoken language or place of birth. Prescriptions and refills for antidiabetic medications were recorded for the two years preceding the index date. Clinical, anthropometric, and comorbidity data were analysed.

Results

Our final cohort consisted of data from 150,237 patients. During up to 20 years of follow-up, 39% of participants developed dementia (crude proportion); however, when accounting for death as a competing risk, the 10-year cumulative incidence was approximately 9–10%, and ethnic differences were attenuated after multivariable adjustment. The use of SGLT-2 and DPP-4 inhibitors was associated with a lower probability of dementia. Specifically, SGLT-2 inhibitors (HR, 0.40; 95% CI, 0.38-0.41), GLP-1 agonists (HR, 0.64; 95% CI, 0.62-0.67), and DPP-4 inhibitors (HR, 0.67; 95% CI, 0.65-0.68 were associated with a reduced risk of dementia-related mortality.

Figure 3. Cox proportional hazards regression of predictors of dementia-related .mortality. Results are presented as hazard ratios (HRs) with 95% confidence intervals



133

Prevalence and outcomes of DKA in type 1 and type 2 DM patients treated and not treated with SGLT-2 inhibitors.

Elena Chertok Shacham[1,2], Sireen Sharif[3], Rageh Tatoor[4], Snait Ayalon[3]
[1]*Medicine, Technion , Israel institute of technology*
[2]*Endocrinology, Emek medical center*
[3]*Research authority, Emek medical center*
[4]*Internal Medicine department A, Emek medical center*

Diabetic ketoacidosis (DKA) is a life-threatening complication occurring in people with type 1 (T1DM) and type 2 diabetes (T2DM). Sodium–glucose cotransporter-2 (SGLT2) inhibitors have raised concern for DKA risk, including euglycaemic DKA (euDKA).

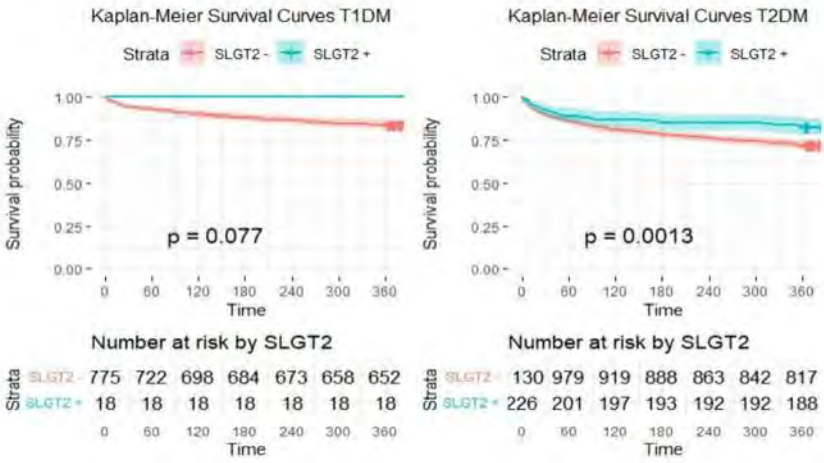
Aim:
To compare the clinical characteristics, biochemical presentation, and short- and long-term outcomes of DKA in hospitalized adults with T1DM and T2DM, including the impact of SGLT2 inhibitor therapy.

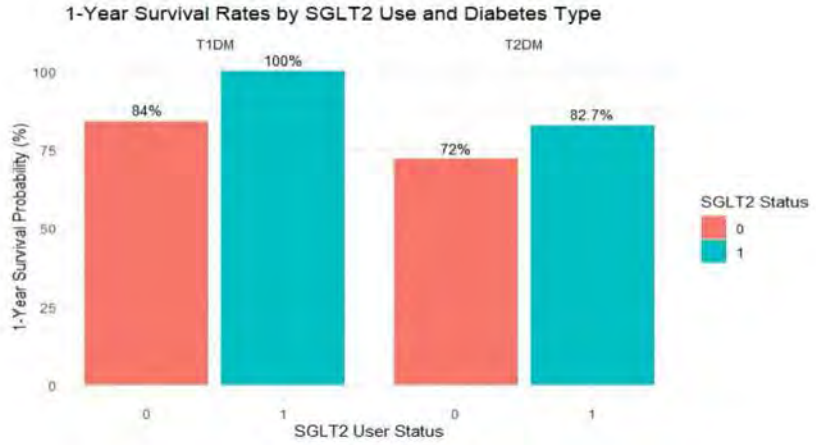
Methods:
A retrospective cohort of 2,283 adults (838 with T1DM; 1,445 with T2DM) hospitalized with DKA between 2013 and 2023 across Clalit Health Services hospitals was analyzed. Patients were stratified by SGLT2 inhibitor use within 4 months before admission. Outcomes included AKI, 30-day mortality, 1-year mortality, and readmissions. One-year mortality was assessed using Cox proportional hazards regression, 30-day mortality using logistic regression, and recurrent readmissions using a negative binomial model.

Results: 2.3% (N=19) of T1DM and 16% (235) of T2DM patients treated with SGLT-2 inhibitors presented with DKA. A total of 115 patients from all cohorts presented with eu DKA, characterized by lower glucose and bicarbonate levels. In T2DM, the incidence of AKI was higher among SGLT2 users (26% vs. 17%; $p = 0.030$), but lower in euDKA cases (9.6% vs. 19%; $p = 0.020$).
In Cox regression analysis, treatment with SGLT2 inhibitors was independently associated with reduced 1-year mortality (HR 0.55, 95% CI 0.36–0.82; $p = 0.004$). Predictors of increased 1-year mortality included older age, higher HbA1c, cardiovascular disease, CKD, and insulin therapy.
In the negative binomial model, higher readmission rates were independently associated with T1DM, higher HbA1c, higher BMI, CKD, and pre-admission insulin use, while SGLT2 inhibitor use was not linked to increased readmissions.

Conclusions:
Pre-hospital SGLT2 inhibitor therapy in patients presenting with DKA was associated with substantially lower long-term mortality and no increase in short-term mortality or readmissions, supporting the safety of these agents when appropriate monitoring is in place.

Figure 1


Kaplan-Meier Survival Curves T1DM
Strata SLGT2 - SLGT2 +
Survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.077
0 60 120 180 240 300 360
Time
Kaplan-Meier Survival Curves T2DM
Strata SLGT2 - SLGT2 +
Survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.0013
0 60 120 180 240 300 360
Time
Number at risk by SLGT2
Strata
SLGT2 - 775 722 698 684 673 658 652
SLGT2 + 18 18 18 18 18 18 18
0 60 120 180 240 300 360
Time
Number at risk by SLGT2
Strata
SLGT2 - 130 979 919 888 863 842 817
SLGT2 + 226 201 197 193 192 192 188
0 60 120 180 240 300 360
Time


1-Year Survival Rates by SGLT2 Use and Diabetes Type
T1DM
T2DM
100%
84%
72%
82.7%
1-Year Survival Probability (%)
100
75
50
25
0
0
1
0
1
SGLT2 User Status
SGLT2 Status
0
1

Delayed puberty and type 2 diabetes risk

Orit Pinhas-Hamiel[1,2], Maya Simchoni[3,4], Estela Derazne[5], Cole D. Bendor[4,5], Avishai M. Tsur[5,6], Adi Vinograd[7,8], Miri Lutski[7,8], Inbar Zucker[5,9], Vibha Singhal[10], Hertzel C. Gerstein[11], Arnon Afek[12], Amir Tirosh[5,13], Gilad Twig[13,14]

[1]*Pediatric Endocrine and Diabetes Division, Edmond and Lily Safra Children's Hospital, Sheba Medical Center* [2]*Department of Medicine, Gray Faculty of Medical & Health Sciences university Department of Military Medicine, Hebrew University, Jerusalem*

[4]*The Israel Defense Forces Medical Corps, Ramat Gan, Israel.*

[5]*Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

[6]*Department of Medicine, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel*

[7]*The Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel*

[8]*Department of Epidemiology and Preventive Medicinel, School of Public Health, Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israe*

[9]*The Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel*

[10]*Division of Endocrinology, Department of Pediatrics, University of California, Los Angeles, CA, USA*

[11]*Department of Medicine, McMaster University, Hamilton, Ontario, Canada*

[12]*The Dina Recanati School of Medicine, Reichman University, Israel*

[13]*Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel Hashomer, Israel*

[14]*Department of Epidemiology and Preventive Medicine, School of Public Health., Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

Background Delayed puberty has been associated with adverse metabolic outcomes, yet longitudinal evidence on its relation to type 2 diabetes risk is scarce. We aimed to investigate the association between delayed puberty during adolescence and early-adult-onset type 2 diabetes in male adolescents.

Methods This nationwide, population-based, retrospective cohort study included Israeli male adolescents aged 16–19 years who were examined before military recruitment during 1992–2015 and followed until Dec 31, 2019. Exclusion criteria were diabetes at the baseline medical assessment, hypogonadotropic hypogonadism, missing height or weight data, and death before the establishment of the Israeli National Diabetes Registry (INDR) in 2012. Delayed puberty was diagnosed by board-certified paediatric endocrinologists, based on physical examinations and laboratory evaluations. By linking data to the INDR, diabetes was identified by: haemoglobin (Hb)A1c concentrations of more than 6.5%, serum glucose concentrations of more than 200 mg/dL in two tests at least 1 month apart, or repeated purchases of glucose-lowering medications. Type 2 diabetes was classified according to medication records, which underwent quality assessment to ensure accuracy. Cox proportional hazards models were applied.

Findings This nationwide, population-based study included 964,108 Israeli male adolescents (mean age at evaluation 17.3 years [SD 0.5]), examined before military recruitment during 1992–2015 and followed until Dec 31, 2019, with a mean age of diagnosis of 35.5 years (SD 5.2). Delayed puberty was diagnosed in 4,307 males and 959,801 did not have delayed puberty. During a cumulative follow-up of 15,242,068 person-years, type 2 diabetes was diagnosed in 111 (2.6%) individuals with delayed puberty and 6,259 (0.7%) individuals without delayed puberty. The respective incidence rates of type 2 diabetes were 140.3 cases per 100,000 person-years (95% CI 114.2–166.4) and 41.3 cases per 100,000 person-years (95% CI 40.3–42.3; p0.0001; absolute difference 99.0 [95% CI 72.9–125.1]). After adjustment for birth year, residential socioeconomic status, cognitive function, education level, and country of birth, delayed puberty was associated with an increased risk of type 2 diabetes (hazard ratio [HR] 2.47 [95% CI 2.04–2.99], p0.0001). Additional adjustment for baseline BMI attenuated but did not eliminate the association (HR 1.37 [95% CI 1.13–1.66]; p=0.0015). The findings persisted across extensive sensitivity analyses.

Interpretation Male adolescents with delayed puberty are at increased risk of developing type 2 diabetes in early adulthood, independent of BMI. These findings suggest that delayed puberty is not a benign developmental variant, but might serve as an early marker of increased risk for later abnormal glucose metabolism.

136

Exploring Changes in Body Composition and Metabolic Risk in Adolescents With Obesity Under GLP-1 Receptor Agonist Therapy

Adar Lopez[1], Liat Perl[1,2], Ophir Borger[1], Yael Issan[1], Hagar Interator[1], Eyal Cohen-Sela[1,2], Erez Azoulay[1], Hadar Moran-Lev[2,3], Ronit Lubetzky[2,3], Yael Lebenthal[1,2], **Avivit Brener**[1,2]

[1]*The Institute of Pediatric Endocrinology, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center*

[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

[3]*The Institute of Pediatric Gastroenterology, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center*

Aim: To explore the changes in body composition in adolescents with obesity treated with glucagon-like peptide-1 receptor agonists (GLP-1 RA) and its association with metabolic syndrome (MetS) components.

Methods: This real-world retrospective cohort study included adolescents with obesity, treated and monitored between 01.2020-12.2024. Routine medical care was provided by a multidisciplinary obesity team and included healthy lifestyle counseling. GLP-1 RA therapy was prescribed to 41 of the 67 participants (61.2%), with individualized management and dosing strategies. Z-scores for BMI and body composition parameters assessed via bioimpedance analysis [appendicular skeletal muscle mass (ASMM) and muscle-to-fat ratio (MFR)] were collected at 3 time points: 6 months prior to GLP-1 RA initiation, at initiation, and during treatment. MetS components (glucose intolerance, hypertension, and dyslipidemia) were evaluated at each visit.

Results: Adolescents receiving GLP-1 RA therapy experienced greater improvements in weight (-6.0[-14.2,2.9] vs. 1.75[-0.3,4.8] kg, P0.001), BMI z-score (-0.34[-0.57,-0.07] vs.−0.07[−0.17,0.05], P0.001), and MFR z-score (0.41[0.12,0.56] vs.0.13[0.01,0.25], P=0.007). Multiple regression analyses adjusted for sex, age, sports activity and follow-up duration identified GLP-1 RA treatment duration as the sole contributor to BMI and MFR z-scores changes (R^2=0.515, P0.001) and (R^2=0.231, P=0.012), respectively. In the overall cohort, 49 participants (73.1%) exhibited at least one MetS component, among whom improvement was observed in 17(34.7%). Logistic regression models found that improvements in BMI and MFR z-scores were linked to an increased likelihood of MetS component improvement.

Conclusions: GLP-1 RA therapy led to improved body composition in adolescents with obesity, contributing to the observed improvement in prevalent MetS components.

Differentiating mouse and human adipose tissue derived fatty acid binding protein 4 (FABP4) in the regulation of cancer growth

Nicole Geller[1,2], Rinat Livne[1], Reem Igbaria[1,2], Amir Tirosh[1,2]
[1]*The Dalia and David Arabov Endocrinology and Diabetes Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center*
[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

There is a growing role for adipose tissue in providing stromal support for tumor development and growth. In many cancers, tumor-surrounding adipocytes support the growing tumor by various secreted factors. Furthermore, adipose tissue dysfunction in obesity is an established risk factor not only for cardio-metabolic abnormalities, but also, as becoming increasingly evident, for increased cancer incidence and aggressiveness. Yet, the complex molecular mechanisms underlying the cancer-obesity link, are not fully understood. Rapidly accumulating evidence suggest that the adipokine fatty acid binding protein 4 (FABP4), is an important facilitator of cancer growth, representing a causal mediator of this crosstalk.

We previously showed that both melanoma and pancreatic ductal adeno-carcinoma (PDAC) cells proliferation and migration are markedly enhanced *in-vitro* by incubation with mouse adipose tissue condition medium, effects that are significantly inhibited when adipose tissue of Fabp4 knockout (*Fabp4*$^{-/-}$) mice is used. Similarly, the *in-vivo* growth of melanoma or PDAC tumors is profoundly attenuated in *Fabp4*$^{-/-}$ compared to wild-type mice. Furthermore, an FABP4 monoclonal antibody developed by us is able to neutralize circulating FABP4 and to inhibit melanoma growth *in-vivo*.

Next, we used a novel mouse model in which the mouse FABP4 (mFABP4) gene was replaced with the human gene (hFABP4). We demonstrate that in this mouse model adipose tissue hFABP4 expression levels as well as FABP4 circulating levels are equivalent to those of mFABP4. In addition, all tested FABP4 metabolic functions were preserved. However, *in-vitro* adipose tissue CM of hFABP4 mice (CM^{hFABP4}) was not able to promote cancer cell proliferation compared to CM of *Fabp4*$^{-/-}$mice ($CM^{-/-}$). In addition, *in-vivo* tumor growth in hFABP4 mice was similar to that of *Fabp4*$^{-/-}$ mice.

Thus, combining these two *in-vivo* models allow us to differentiate between FABP4 metabolic and malignant functions in order to delineate the host FABP4 components that are relevant for promoting cancer growth.

138

The effects of 10 weeks of time-restricted eating, resistance training, and their combination on body fat depots and low-grade inflammation in patients with metabolic syndrome

Roi Yavetz[1,2], Ron Sternfeld[1,2], Yair Lahav[1,2], Michal Rein[3], Shira Zelber Sagi[3], Hasan Ishtayeh Ishtayeh[4], Avraham Ashkenazi[4], Nir Polak[5], Shai Efrati[5], Yftach Gepner[6,7]

[1]*Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Gepner Lab*

[2]*Tel Aviv University, Sylvan Adams Sport Institute*

[3]*University of Haifa, School of Public Health*

[4]*Tel Aviv University, Sagol School of Neuroscience*

[5]*Shamir Medical Center (Assaf Harofeh), Sagol Center for Hyperbaric Medicine and Research*

[6]*Department of Epidemiology and Prevention Medicine, School of Public Health, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Gepner Lab*

[7]*Tel Aviv University, Sylvan Adams Sport Science Institute*

Introduction: Visceral adipose tissue (VAT), hepatic fat content (HFC), and chronic low-grade inflammation are key markers of metabolic syndrome (MetS). While time-restricted eating (TRE) and resistance training (RT) individually improve metabolic health by reducing VAT, HFC, and inflammatory markers like IL-6, TNF-α, and leptin, their combined effects in MetS patients are not well understood.

Objectives and Hypothesis: This study aimed to evaluate the effects of TRE, RT, and their combination on VAT, HFC, and inflammatory markers in MetS. We hypothesized that combined TRE+RT would demonstrate synergistic effects, leading to superior improvements compared to TRE alone.

Methods: Seventy-six adults with MetS (mean age: 50.4 years, mean BMI 31.4 kg/m²) were randomized for 10 weeks into three groups: normal diet + resistance training (ND+RT), time-restricted eating + resistance training (TRE+RT), and TRE only. All participants consumed isocaloric diets with 1.5 g/kg/day of protein. TRE groups adhered to an eight-hour eating window (12:00 pm - 8:00 pm); RT groups performed supervised resistance training three times weekly. VAT and HFC were assessed via MRI and MRS, and serum levels of IL-6, TNF-α, and leptin were measured pre- and post-intervention.

Results: The TRE+RT group showed a significant decrease in VAT compared to TRE only (-107±55 cm³, p=0.04), and the most significant reduction in HFC (-3.8±1.3%, p=0.007). Only TRE+RT had significant declines in IL-6 (-0.36±0.53 pg/ml, p=0.01) and TNF-α (-0.74±1.3 pg/ml, p=0.01) from baseline, with greater reductions than TRE only (p=0.01 for IL-6 and p=0.03 for TNF-α). Leptin levels decreased significantly in both ND+RT and TRE+RT groups, with TRE+RT showing significant reductions compared to TRE only (p=0.03).

Conclusion: Combining TRE and RT leads to greater reductions in VAT, HFC, and inflammatory markers, including leptin, IL-6, and TNF-α, compared to TRE alone. These findings highlight the synergistic benefits of integrating these interventions in managing metabolic syndrome.

Fig1.3D visualization using meidcal imaging software of HFC where brighter areas indicate higher fat

Fig2.3D visualization using meidcal imaging software of VAT with yellow-highlighted regions representing VAT.

139

Integrating Amniotic Manganese and Machine Learning for LGA Prediction: A Prospective Mother-Fetus-Newborn Cohort Study

Yaniv Ovadia[1,2], Abigail Paradise Vit[3], Ishai Dror[2], Brian Brian Berkowitz[2], Efraim Zohav[4,5], Gad Liberty[4,5]

[1]*Obstetrics and Gynecology Division, Barzilai University Medical Center, Ashkelon, Israel.*

[2]*Department of Earth and Planetary Sciences, Weizmann Institute of Science, Rehovot, Israel*

[3]*Department of Information Systems, The Max Stern Emek Yezreel College, Emek Yezreel, Israel*

[4]*Obstetrics and Gynecology Ultrasound Unit, Barzilai University Medical Center Ashkelon, Israel*

[5]*Faculty of Health Sciences, Ben-Gurion University of Negev, Ashkelon, Israel*

Background

Large-for-gestational-age (LGA) newborns, defined as birth weights above the 90th percentile for gestational age, are at elevated risk for perinatal complications and long-term metabolic disorders, including childhood and adult obesity, insulin resistance, and type 2 diabetes. These outcomes align with fetal programming hypotheses, where intrauterine exposures contribute to lifelong obesity risk. Accurate prenatal prediction of LGA remains challenging, particularly in low-risk pregnancies, highlighting the need for novel biomarkers integrating maternal-fetal factors and trace elements.

Objectives

This study evaluated the feasibility of a machine learning (ML) model incorporating mid-pregnancy amniotic fluid elemental concentrations, including manganese (Mn), with established maternal and fetal risk factors to predict LGA newborns—a key prenatal marker of future obesity risk—in a prospective mother-newborn cohort.

Methods

In a prospective observational study at Barzilai University Medical Center (July 2020–October 2024), 221 complete mother-newborn pairs were recruited. Amniotic fluid elemental concentrations, including Mn, were quantified via inductively coupled plasma mass spectrometry. Maternal demographics, clinical history, and fetal anthropometric data were recorded. A C5.0 decision tree model was built using 41 features, with recursive feature elimination identifying 14 key predictors. The dataset was divided into 80% training, 10% validation, and 10% testing sets, applying Random Over-Sampling Examples resampling to manage class imbalance (14.93% LGA cases).

Results

Recruitment occurred at a mean gestational age of 19.5 ± 2.5 weeks. On the test set, the C5.0 model yielded an accuracy of 0.863 (95% CI: 0.735–0.943) and an F-score of 0.400 for LGA prediction. Mid-pregnancy amniotic fluid Mn concentrations showed a significant positive correlation with birth weight percentile (P = 0.049, 95% CI: 0.002–0.096), remaining robust after adjustment for maternal age, height, hypothyroidism, diabetes, and parity. LGA newborns exhibited significantly higher median Mn levels than appropriate-for-gestational-age newborns (Kruskal-Wallis test, P = 0.047).

Conclusions

This ML model, integrating amniotic fluid Mn with maternal-fetal factors, offers promising predictive performance for LGA newborns and highlights a significant association between mid-gestational Mn exposure and elevated birth weight. Given LGA`s established link to long-term obesity risk via developmental programming, these findings suggest potential roles for trace elements in fetal metabolic imprinting. Moderate model specificity warrants refinement through larger, multicenter cohorts to enhance clinical utility in obesity prevention strategies.

140

Daily Goitrogen Intake Does Not Impair Thyroid Function or Iodine Status in Euthyroid Pregnant Women with Mild-to-Moderate Iodine Deficiency: Machine Learning-Based Study

Yaniv Ovadia[1], Abigail Paradise Vit[2], Simon Shenhav[1,3]
[1]*Obstetrics and Gynecology Department, Barzilai University Medical Center, Ashkelon, Israel*
[2]*Information Systems Department, The Max Stern Yezreel Valley College, Emek Yezreel, Israel*
[3]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel*

Background

Mild-to-moderate iodine deficiency (ID) persists in several high-income countries without universal salt iodization, including Israel, despite adequate iodine intake being essential for thyroid hormone synthesis during pregnancy. Maternal thyroid dysfunction or suboptimal iodine status might incease the risk for adverse pregnancy outcomes. Goitrogen-containing foods could theoretically exacerbate ID by interfering with iodine uptake and thyroid function, yet evidence in pregnant women remains limited, particularly in regions with mild-to-moderate ID.

Objectives

To (a) assess associations between daily dietary goitrogen intake and iodine status and thyroid function, and to (b) identify key predictors of elevated thyroglobulin using a machine-learning approach.

Methods

This secondary analysis of used data from prospective cohort of euthyroid pregnant women (n=193) from southern Israel were evaluated using a validated iodine-specific food frequency questionnaire, spot urinary iodine concentration (UIC), serum thyroglobulin (Tg), and thyroid function tests. Daily intake of goitrogen-rich foods (mainly almonds, cruciferous vegetables, millet, and flaxseed) was quantified via structured questionnaire and dichotomized (present vs. absent). A bootstrap forest machine-learning model assessed predictors of elevated Tg.

Results

Median UIC and estimated iodine intake were 57 μg/L and 179 μg/d, indicating mild-to-moderate ID. Daily goitrogen consumption was reported by 15% of participants and linked to higher estimated iodine intake and greater iodine supplement use, but not to Tg levels, UIC, TSH, subclinical hypothyroidism, or isolated hypothyroxinemia. The machine-learning model identified low iodine intake and advanced maternal age as primary drivers of higher Tg, with minimal contribution from daily goitrogen intake.

Conclusions

In euthyroid pregnant women with mild-to-moderate ID, typical levels of daily goitrogen consumption do not significantly impair iodine status or thyroid function. Ensuring iodine adequacy remains the key priority to support optimal maternal thyroid function, potentially mitigating risks of altered maternal thyroid function. These findings underscore balanced plant-based nutrition with focus on iodine, filling an important evidence gap for maternal dietary counseling.

141

Explainable AI for personalized Prediction of Adherence to Drug Therapy in People with Type 2 Diabetes: a Nationwide Retrospective Cohort

Michal Kasher Meron[1,2], Riad Taher[3,4], Adi Berliner[4], Eitan Bachmat[5], Doron Levinson[5]
[1]*Endocrinology, Meir Medical Center*
[2]*Gray Faculty of medical and Health Sciences, Tel Aviv University*
[3]*Endocrinology, Rambam Medical Center*
[4]*Clalit Health Services*
[5]*Department of Computer Science, Ben-Gurion University*

Background and Aims

Poor adherence to anti-diabetic therapy is a major barrier to effective disease management, leading to poorer outcomes and increased healthcare costs. Reasons for poor adherence may differ, and may relate to characteristics of patient, disease, therapy and health care system. We present a novel approach for predicting medication non-adherence in patients with type 2 diabetes that combines domain expertise with advanced machine learning to enhance interpretability and explainability.

Materials and Methods

We retrospectively analyzed data from Israel's largest healthcare organization. Included were people with type 2 diabetes, who were prescribed at least one oral anti-diabetic medication and had at least two drug purchases between January 2021 and December 2022. Medication adherence was assessed using the prescription-based Medication Possession Ratio (pMPR), with poor adherence defined as pMPR 0.8. Clinical and administrative features were extracted at baseline. Feature grouping - informed by domain expertise - classified features as reflecting patient general health, healthcare utilization, service accessibility, therapy complexity, and self-care, among others. A light gradient boosting machine model was developed to predict poor adherence, and SHapley Additive exPlanations (SHAP) were used to derive feature importance scores within clinically relevant categories. Clustering methods revealed distinct patient profiles based on SHAP-derived adherence patterns.

Results

The study cohort included 207,062 patients with type 2 diabetes. Overall, 49.3% were female, 70.7% were Jewish, with a mean age of 67.2 ± 11.3 years and a mean pMPR of 0.74 ± 0.29. The machine learning model achieved an AUROC of 0.86 (95% CI: 0.85–0.86). Clustering revealed nine distinct clusters, with three clusters (Clusters 0, 1, and 2) showing high rates of poor adherence (90.4%, 90.2%, and 81%, respectively). In Cluster 0, the feature with the most dominant negative SHAP effect on adherence was the presence of diabetes-related complications and uncontrolled glucose levels. In Cluster 1, negative SHAP values were primarily driven by socioeconomic factors and treatment complexity, while in Cluster 2, system-level factors and limited healthcare accessibility had the strongest negative impact on adherence.

Conclusion

This proof-of-concept study demonstrates that integrating feature grouping with SHAP-derived clustering can identify distinct adherence profiles. This approach may offer valuable insights into barriers to medication adherence at individual and population levels, informing personalized interventions to improve pharmacotherapy adherence in diabetes care.

142

Angiogenic Factors for Prediction of Adverse Outcomes in Pregnancies Complicated by Isolated Fetal Growth Restriction

Ehud Barhod[1], Uri Shemesh[2], Keren Zloto[2], Itay Manor[2], Sharon Kronkop[2], Tal Dadon[2], Rakefet Yoeli[2], Abraham tsur[2], Shali Mazaki-Tovi[2], Rina Hemi[1], Yoav Yinon[2], Michal Fishel-Bartal[2], Noa Gonen[2]

[1]*Endocrine Laboratory, Division of Endocrinology, Diabetes, and Metabolism, Sheba Medical Center*

[2]*Department of Obstetrics and Gynecology, Sheba Medical Center*

Objective: To evaluate whether abnormal sFlt-1/PlGF ratio predicts latency to delivery and development of hypertensive disorders of pregnancy (HDP) among individuals presenting with fetal growth restriction (FGR).

Study Design: A retrospective study including individuals at ≥ 23 weeks presenting to a tertiary care center with suspected FGR (

Results: Of 104 patients with suspected FGR, 36 (34.6%) had an abnormal ratio of sFlt-1/PlGF (≥38). Those with abnormal sFlt-1/PlGF levels were more likely to be nulliparous compared to those with normal testing. The rate of HDP was higher among those with abnormal sFlt- 1/PlGF ratio (30.6% Vs 2.94%, p<0.01, OR 14.5 (3-70.2)) with a shorter median latency from test to delivery (20 vs 36 days, p<0.01) compared to normal testing. Furthermore, those with abnormal sFlt- 1/PlGF ratio delivered earlier (35.4 vs. 37.1, p<0.01) with a lower birthweight (1876 vs 2182 gram, p<0.01) compared to those with normal testing.

Conclusion: Abnormal sFlt-1/PlGF ratio in normotensive individuals with suspected FGR may predict short interval to delivery, development of HDP and adverse perinatal outcomes.

146

A Role for Foxl2 in Maintaining Open Chromatin at a Lineage-Specific Distal Regulatory Element of the *Fshb* Gene

Daniella Darsa[1], Gil Golan[1], Tal Refael[1], Lilach Pnueli[1], Philippa Melamed[1]
Faculty of Biology, Technion-Israel Institute of Technology

Fsh deficiency contributes to infertility, yet the molecular mechanisms governing Fshb gene regulation remain incompletely understood. Our lab has shown that *Fshb* expression is regulated by distal cis-regulatory elements located within a large gene desert. Multi-omics (scRNA-seq and scATAC-seq) during differentiation of gonadotropes from neonatal pituitary stem cells, revealed that these elements are located in chromatin which is accessible in mature gonadotropes and partly open also in pituitary stem cells, though not in the other hormone-producing cell types. The locus has characteristics of a “super-enhancer” and is bound by Foxl2, a crucial transcription factor known to bind and activate the Fshb gene promoter. However the role of Foxl2 in regulating Fshb expression via this upstream site, and any effects in shaping the chromatin landscape at thelocus are not known. Here, we tested the hypothesis that Foxl2 binding at the distal *Fshb* super-enhancer plays a role in maintaining a state of open chromatin.

Using CRISPR-Cas9 editing in murine αT3-1 gonadotrope cells, we generated a biallelic Foxl2 knockout clone exhibiting complete loss of Foxl2 protein. We assessed chromatin accessibility by quantifying histone H3 occupancy as a measure for nucleosome density. The ChIP-qPCR was performed across six genomic regionsspanning the enhancer, located between -66.9 kb to -68.0 kb upstream of the *Fshb* transcription start site(TSS).

We found that complete loss of Foxl2 led to significantly increased (P 0.05) association of histone H3 across the region between -67,400 to -68,052 bp upstream of the *Fshb* TSS, consistent with increased nucleosome occupancy and reduced accessibility. In contrast, no difference in H3 occupancy was observed at the *Atoh* control locus. These findings align with our multi-omic data of the events during gonadotrope differentiation, and indicate that Foxl2 contributes to preserving chromatin accessibility at a lineage-specific distal regulatory element of the *Fshb* locus.

147

First-Visit Anti-Obesity Medication Recommendation and One-Year Patient Retention and Weight Loss

Dekel Homossany[1], Michael Rechter[2], Liat Barzilai-Yosef[2], Pnina Rotman-Pikielny[1,2], Michal Kasher Meron[1,2]

[1]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

[2]*Endocrinology, Meir Medical Center*

Objectives: Physicians vary in whether they document anti-obesity medication recommendations at the initial visit. We examined whether first-visit medication recommendation documentation is associated with one-year patient retention and weight loss.

Methods: This retrospective cohort study analyzed patients with newly diagnosed obesity at the Meir Endocrinology Institute (January 2019–December 2022). Patients were categorized by whether anti-obesity medication (specific drug name and dosage) was documented in the initial visit note. The primary outcome was clinic attendance with documented weight measurement at 9–15 months; the secondary outcome was ≥5% weight loss from baseline. Logistic regression models assessed associations adjusted for age, sex, distance from clinic, baseline BMI, and comorbidities. Medication recommendations at subsequent visits and actual medication dispensing or use were not assessed.

Results: Among 422 patients, 278 (65.9%) had anti-obesity medication documented in the initial visit note. Overall, 130 patients (30.8%) completed one-year follow-up, with similar rates between groups (52.2% with vs. 55.3% without first-visit medication documentation; adjusted OR: 1.29, 95% CI: 0.81–2.05, p=0.29). Among all patients, 69 (16.4%) achieved ≥5% weight loss, with no significant difference by first-visit medication documentation status (adjusted OR: 0.85, 95% CI: 0.39–1.88, p=0.69). Younger age, proximity to clinic, and female sex independently predicted both retention and weight loss.

Conclusions: First-visit anti-obesity medication documentation was not associated with one-year patient retention or weight loss. Patient demographic and logistical factors were stronger predictors of both outcomes.

148

Neurodegeneration onset with glucagon-like peptide-1 receptor agonists in people with type 2 diabetes: a real-world multinational cohort study

Meir Schechter[1,2], Alisa Fishkin[1,2], Ofri Mosenzon[2,3], Dvora R Sehtman-Shachar[1,2], Tali Cukierman-Yaffe[4,5], Gil Leibowitz[1,2], Genya Aharon-Hananel[1,2]

[1]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel*

[2]*Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*

[3]*Regeneron Pharmaceuticals Inc., New York, New York, USA*

[4]*Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel*

[5]*Department of Epidemiology and Preventive Medicine, School of Public Health, Dear Gray Faculty of Medical and Health Sciences, Tel-Aviv University, Tel Aviv, Israel*

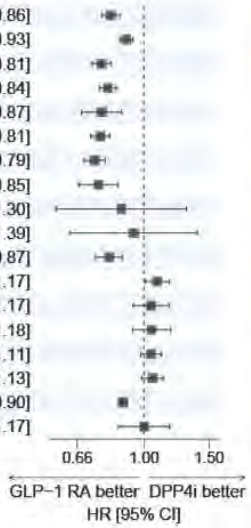
Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been proposed to possess neuroprotective properties. Preliminary data from the phase 3 EVOKE/EVOKE+ placebo-controlled trials program indicate that 2-year treatment with oral semaglutide, although improving Alzheimer`s-related biomarkers, did not prevent disease progression, in people with early Alzheimer`s disease, mostly without type 2 diabetes (T2D). It remains unclear whether in people with T2D without neurodegeneration, GLP-1 RAs may prevent the onset of neurodegeneration.

Methods: In this retrospective cohort study, we used the TriNetX global platform, which contains electronic health records of over 170 million people worldwide. We propensity-score matched (1:1) individuals with T2D who lacked any evidence of neurodegeneration and initiated GLP-1 RAs or dipeptidyl peptidase-4 inhibitors (DPP4i) (2010-2021). In a separate analytical cohort, we compared individuals initiating GLP-1 RA with those initiating basal insulin. Follow-up continued for ≤5 years. We used Cox proportional-hazard regression models to assess the risk of the composite outcome of developing new neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, dementia subtypes, and other synucleinopathies. We also assessed each component individually. Analyses were repeated among subgroups defined by sex, age, and the specific GLP-1 RA initiated.

Results: Overall, 214,442 matched individuals initiated GLP-1 RAs or DPP4i (109,731 women, mean age 58.6 years [SD 12], and mean HbA1c 7.7% [1.4]). During a 4.0-year mean follow-up, neurodegenerative disorder onset occurred in 2,393 (2.2%) and 3,062 (2.9%) people initiating GLP-1 RAs and DPP4i, respectively (hazard ratio of 0.81 [95% CI 0.77-0.86]; absolute risk difference -0.6% [-0.8 – -0.5]). The associations were separately observed among women (0.78 [0.72-0.84]) and men (0.90 [0.83-0.98]), individuals aged ≥65 years old (0.82 [0.78-0.87]) or or 65 years old (0.84 [0.70-1.00]), and in those initiating semaglutide (0.75 [0.67-0.84]), liraglutide (0.77 [0.70-0.84]), or dulaglutide (0.82 [0.77-0.88]). The hazard ratios for dementia, Alzheimer`s disease, vascular dementia, and Parkinson`s disease onset were 0.76 [0.72-0.81], 0.77 [0.68-0.87], 0.75 [0.67-0.85], and 1.04 [0.93-1.17] with GLP-1 RAs versus DPP4i, respectively (**figure**). The results were similar when comparing individuals initiating GLP-1 RAs with those initiating basal insulin.

Conclusions: In a real-world cohort of people living with T2D with global representation, initiation of GLP-1 RAs, compared with DPP4i or basal insulin, was associated with a lower risk of new-onset neurodegeneration. These data support the rationale for dedicated clinical trials to assess the potential neuroprotective properties of GLP-1 RAs in this population.

Outcome	GLP−1 RA n(%)	DPP4i n(%)	HR [95%CI]
Neurodegenerative disease onset	2393 (2.2%)	3062 (2.9%)	0.81 [0.77−0.86]
Neurodegenerative disease onset or drug initiation	4150 (3.9%)	4783 (4.5%)	0.90 [0.86−0.93]
Alzheimer's or dementia onset	1939 (1.8%)	2632 (2.5%)	0.77 [0.72−0.81]
Alzheimer's or dementia onset, or dementia drugs initiation	2360 (2.2%)	3073 (2.9%)	0.80 [0.76−0.84]
Alzheimer's onset	427 (0.4%)	586 (0.5%)	0.77 [0.68−0.87]
Dementia onset	1899 (1.8%)	2598 (2.4%)	0.76 [0.72−0.81]
Unspecified dementia onset	1578 (1.5%)	2240 (2.1%)	0.74 [0.69−0.79]
Vascular dementia onset	434 (0.4%)	603 (0.6%)	0.75 [0.67−0.85]
Dementia with Lewy bodies onset	42 (0.04%)	52 (0.05%)	0.87 [0.58−1.30]
Frontotemporal dementia onset	46 (0.04%)	52 (0.05%)	0.94 [0.63−1.39]
Initiation of drugs for dementia	987 (0.9%)	1280 (1.2%)	0.80 [0.74−0.87]
Mild cognitive impairment onset	1317 (1.2%)	1266 (1.2%)	1.09 [1.01−1.17]
Synucleinopathy onset	614 (0.6%)	615 (0.6%)	1.04 [0.93−1.17]
Parkisnon's onset	545 (0.5%)	543 (0.5%)	1.05 [0.93−1.18]
Parkinson's onset or Parkinson's drugs initiation	1960 (1.8%)	1934 (1.8%)	1.04 [0.98−1.11]
Initiation of drugs for Parkinson's	1725 (1.6%)	1684 (1.6%)	1.05 [0.99−1.13]
New onset stroke or death (positive control)	10454 (10.6%)	12371 (12.5%)	0.88 [0.86−0.90]
Acute appendicitis (negative control)	300 (0.3%)	309 (0.3%)	1.00 [0.85−1.17]



The risk of experiencing the onset of each of the neurodegenerative-related outcomes in people living with type 2 diabetes without prior neurodegeneration initiating GLP-1 RAs compared to those initiating DPP4 inhibitors

Legends: The main outcome was a composite of all tested neurodegenerative disorders, comprising a new diagnosis of Alzheimer's disease, Parkinson's disease, any synucleinopathy, or any dementia. Another composite outcome consisted of a diagnosis of neurodegenerative disorders or the initiation of a drug to treat dementia or Parkinson's disease. We also evaluated the risk of new-onset diagnosis of Alzheimer's disease, Parkinson's disease, any dementia, vascular dementia, other or unspecified dementia, frontotemporal dementia, dementia with Lewy bodies, a composite of any synucleinopathy, mild cognitive impairment, initiation of treatment for dementia, and initiation of treatment for Parkinson's disease. We assessed the composite outcome of a new stroke or death as a positive control and acute appendicitis as a negative control.

adding long-acting insulin to automated insulin delivery systems among youth with type 1 diabetes may prevent ketoacidosis events: a case series

Libby Shopen[1,2], Gila Lavy[1], Shira Harel[3,4], Zohar Landau[4], Shirly Abiri[2,5], Marianna Rachmiel[1,2]

[1]*Pediatric Endocrinology and Diabetes Institute, Shamir (Assaf Harofeh) Medical Center, Beer Yaakov, Israel*

[2]*Grey Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

[3]*Pediatric Endocrine and Diabetes Unit, Assuta Medical Center, Ashdod, Israel*

[4]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*

[5]*Pediatric Endocrinology Unit, Edith Wolfson Medical Center, Holon, Israel*

Background: Advanced hybrid closed loop (AHCL) systems have substantially improved glycemic control and reduced diabetes burden among adolescents with type 1 diabetes (T1D). Nevertheless, concerns regarding diabetic ketoacidosis (DKA), the need for sustained vigilance and dose limitations may restrict their use. The addition of long-acting insulin to an open-pump therapy was proposed as a safety strategy among poorly controlled populations, with reported DKA prevention.

Objective: To describe real life experience of combining once daily long-acting insulin injections in addition to AHCL system in clinical practice.

Methods: A case series of patients using AHCL systems, in whom the clinical teams decided to add a daily long-acting insulin injection while reducing basal insulin delivery via the pump (Combination Modality). Data was extracted from medical records and pump/continuous glucose monitoring (CGM) platforms at initiation of combination therapy and after at least four months of follow-up. Outcome parameters included glycemic control parameters, emergency department (ED) visits due to hyperglycemia and DKA events.

Results: 11 patients [(72.7% males, median age 13.8 years)IQR 11.0,16.3)] with median socioeconomic position (SEP) cluster 5 (IQR 3,7) and SEP index -0.13 (IQR -0.76, 0.63), were treated with the combination modality for a median of 6 months (IQR 5.5,6.5). 8 patients were using the Medtronic MiniMed™ 780G hybrid closed-loop system, two were using the Tandem t:slimX2 pump, and one was using an Omnipod pump via DIY system. Indications for Combination Modality included episodes of DKA and ED visits due to hyperglycemia while using AHCL system alone, fear of such events, and DIY-Omnipod with high total daily insulin requirements. No statistically significant difference was observed in HbA1c, TIR, or ED visits/month or DKA events/month. However, seven of ten patients showed HbA1c improvement, with a median reduction of 1.0% (IQR 0.7–1.25). Four of five patients with prior DKA remained DKA-free during combination therapy.

Conclusion: Combination Modality of daily long-acting insulin and AHCL system is a safe and valuable tool in specific circumstances, for prevention of DKA events among selected patients (low SEP, lack of continuous parental supervision), and for enabling use of AHCL among those requiring high TDD of insulin and preferring tubeless pumps. These findings underscore the importance of personalized diabetes management, in the era of advanced technologies.

150

Distinct Phenotype of Severe, Treatment-Resistant Obesity Associated With Heterozygous Pathogenic Variants in the Melanocortin Pathway

Noga Minsky[1,2], Oran Rahamim[3], Odelia Chorin[2,4], Dror Dicker[2,5], Gabriella Segal-Lieberman[1,2]

[1]*Division of Endocrinology, Diabetes and Metabolism Sheba Medical Center, Israel*
[2]*Gray School of Medicine, Tel-Aviv University, Israel*
[3]*School of Medicine, University of Nicosia, Cyprus*
[4]*The Danek Gertner Institute of Genetics, Sheba Medical Center*
[5]*Internal Medicine, Hasharon Hospital, Israel*

Background

Rare genetic variants affecting the melanocortin (MC4R) appetite-regulating pathway can cause early-onset hyperphagia and severe obesity, yet adult recognition remains limited. Identifying adults with pathogenic variants may enable precision therapies, but the clinical value of targeted screening is uncertain. We evaluated phenotypic features associated with pathogenic variants to inform adult screening strategies.

Methods

Non-pregnant adults (≥19 years) with BMI ≥40 kg/m² and childhood-onset obesity with hyperphagia underwent genetic screening through the ROAD program using an 80-gene MC4R-pathway panel at two hospital-based obesity clinics in central Israel. Clinical, anthropometric, and demographic data were abstracted from medical records. Variants were interpreted per ACMG guidelines with expanded reclassification. Group comparisons used t-tests and Fisher's exact tests ($p \leq 0.05$).

Results

Eighty-five adults were screened (May 2022–January 2024); 78 were included after excluding variants of uncertain significance. Fourteen participants (17.9%) carried heterozygous pathogenic/likely pathogenic (P/LP) variants; 64 had negative/benign results (Table 1). One P variant reflected an autosomal-dominant syndrome (16p11.2 deletion) with concordant features; two individuals carried multiple P/LP variants. Compared with negative screens, P/LP carriers had markedly higher BMI (58.0±19.0 vs 48.6±10.9 kg/m²; p=0.01) and were older (47.7±15.6 vs 37.6±13.8 years; p=0.02) (Table 2). Notably, they were threefold more likely to have undergone bariatric surgery (57.1% vs 17.2%; p=0.004), yet BMI remained higher, suggesting treatment-resistant obesity. There were no differences in sex, anti-obesity medication use (including GLP-1 receptor agonists), bariatric procedure type, cardiometabolic comorbidities, psychiatric diagnoses, or family history of obesity.

Conclusions

In adults with severe, childhood-onset obesity, targeted MC4R-pathway screening identified pathogenic variants in ~16–18% of patients. The key novel finding is a distinct adult phenotype characterized by substantially higher BMI despite greater exposure to bariatric surgery, indicating more severe, treatment-resistant disease. These results support consideration of genetic testing in adult to guide precision therapies, particularly those with inadequate response to bariatric surgery. Prospective, longitudinal studies with broader genomic coverage are needed to refine screening criteria and therapeutic implications.

Table 1. Variants Associated with Obesity

Genomic sequence	Amino acid sequence	Interpretation[1]
del 16p11.2	–	Pathogenic
CEP290:c.4882C>T	Gln1628*	
BBS2: c.1895G>C	Arg632Pro	
POMC: c.427C>T	His143Tyr	
PCSK1: c.661A>G[2]	Asn221Asp	Likely pathogenic
PCSK1: c..295G>A	Ala99Thr	
MC3R: c.35C>T[3]	Pro12Leu	
PCSK1: c..295G>A	Ala99Thr	
VPS13B: c.6802G>T	Glu2268*	
RAB23: c.203dup	Glu69Glyfs*4	
NPR2: c.1594G>A	Gly532Ser	
MRAP2: c.228-2A>G	Splicing	
PLXNA3: c.883G>A	Ala295Thr	
SEMA3A: c.2046dup	Gly683Trpfs5*	
DNMT3A: c.1372C>T	Arg458Trp	
PLXNA2: c.4653G>A	Met1551Ile	

	Pathogenic / likely pathogenic (n=14)	Negative / benign / likely benign (n=64)	P value
Age (years)	47.7 ± 15.6	37.6 ± 13.8	0.02*
Male sex	7 / 14 (50.0)	30 / 64 (46.9)	> 0.99
BMI (kg/m^2)	58.0 ± 19.0	48.6 ± 10.9	0.01*
Bariatric surgSery	8 / 14 (57.1)	11 / 64 (17.2)	0.004*
AOM use	11 / 14 (78.6)	54 / 64 (84.4)	0.7
GLP-1RA use	10 / 14 (71.4)	48 / 64 (75.0	0.7
Diabetes	3 / 13 (23.1)	13 / 59 (22.0)	> 0.99
HTN	5 / 13 (38.5)	14 / 38 (36.8)	> 0.99
Dyslipdemia	8 / 11 (72.7)	28 /46 (60.9)	0.79
OSA	6 / 13 (46.2)	20 / 48 (41.7)	> 0.99
MASLD	8 / 13 (61.5)	21 / 44 (47.7)	0.53
ADHD	0 / 14 (0)	10 /64 (15.6)	0.19
Dyslexia	1 / 13 (7.7)	1 / 56 (1.8)	0.34
Psychiatric diagnosis	2 / 13 (15.4)	12 / 56 (21.4)	0.72
Psychaitric medication use	3 / 14 (21.4)	12 / 63 (19.1)	> 0.99
Eating disorders	1 / 14 (7.1)	12 / 51 (25.5)	0.27
FH obesity	8 / 11 (72.7)	41 / 55 (74.6)	> 0.99

Table 2. Positive vs. Negative Screening

151

The Effect of Pancreatic Exocrine Replacement Therapy on Diabetic Patients with Pancreatic Exocrine Insufficiency

Yousef Shukha[1,2], Shadi Hamoud[2,3], Afif Nakhleh[1,4], Naim Shehade[4,5]
[1]*Endocrinology, Diabetes, and Metabolism Unit, Rambam Health Care Campus*
[2]*Internal Medicine E Department, Rambam Health Care Campus*
[3]*Rappaport Faculty of Medicine, Technion, Israel Institute of Technology*
[4]*Diabetes and Endocrinology Clinic, Maccabi Healthcare Services*
[5]*SPHERE Project, The Azrieli Faculty of Medicine, Bar-Ilan University*

Background: Pancreatic Exocrine Insufficiency (PEI) is a well known and bothersome consequence of different diseases involving the pancreas, but also appears in decent percentages among type 2 diabetes mellitus (T2DM) patients. Symptoms may vary from mild to severe cases of abdominal discomfort, bloating, increased flatulence and steatorrhea. Fecal Elastase-1 measurement and clinical patient reported PEI questionnaire (PEI-Q) are two different validated methods currently used for diagnosing PEI. Limited data is available regarding the impact of pancreatic enzyme replacement therapy (PERT) on the quality of life, symptoms and even glycemic measures among diabetic subjects with PEI.

Aim: We aim to examine the effect of PERT (Pancreatin- Creon) on T2DM patients diagnosed with PEI according to the PEI-Q score. In addition, we plan to assess the correlation between the PEI-Q scores and fecal elastase-1 levels for the diagnosis of PEI and the correlation between PEI-Q scores and glycemic indices before and after the treatment.

Methods: In a open-label phase IV prospective cohort study, 25 T2DM patients diagnosed with PEI according to PEI-Q, received PERT for 3 months after undergoing blood examinations for HbA1C, fasting glucose and lipid profile in addition to stool elastase-1 test. A follow-up visit after the 3 month treatment period included blood examinations for the same indices along with another PEI-Q.

Results: Compared to pre-treatment, patients reported significant clinical improvements associated with markedly improved questionnaire scoring (P-Value 0.001). In addition, PEI-Q showed high sensitivity compared to Fecal-Elastase-1 test in diagnosing PEI. No adverse effects were reported.

Conclusion: PEI-Q and PERT represent safe and effective means to diagnose and treat diabetic patients with PEI.

152

Pregnancy-Induced Cushing Syndrome: Diagnosis and Management of a Rare Endocrine Disorder

Ronit Koren[1,2], Efrat Markus[3], Yifat Wiener[2,4], Yona Greenman[2,5], Shlomit Koren[2,3]
[1]*Department of Internal Medicine A, Shamir Medical Center, Zerifin, Israel*
[2]*Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Endocrine Institute, Shamir medical center, Zerifin, Israel*
[4]*Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Zerifin, Israel*
[5]*Institute of Endocrinology, Metabolism, Diabetes and Hypertension, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel.*

Introduction:
Endogenous Cushing syndrome (CS) during pregnancy is a rare condition associated with substantial maternal and fetal morbidity and mortality. Pregnancy-induced Cushing syndrome (PICS) represents an exceptionally rare subtype, resulting from aberrant expression of luteinizing hormone (LH) and/or human chorionic gonadotropin (hCG) receptors on adrenal cortical cells. We report a case of PICS without detectable adrenal abnormalities on imaging, successfully managed with medical therapy until delivery.

Case Report:
A 25-year-old woman presented at 26 weeks of gestation with newly diagnosed hypertension. Physical examination revealed severe acne, hirsutism, a dorsocervical fat pad, and extensive violaceous striae over the abdomen, arms, and legs. Biochemical evaluation demonstrated markedly elevated urinary free cortisol (UFC) levels (1,659 µg/24h; reference range 13–75 µg/24h). Serum cortisol concentrations were significantly elevated in the morning (47.56 µg/dL) and remained unsuppressed at midnight (47.12 µg/dL). Midnight salivary cortisol was 3 µg/dL (reference

Pituitary, adrenal, and ovarian imaging revealed no pathological findings. Medical treatment with metyrapone was initiated and gradually titrated to 2 g/day. Additional therapies included unfractionated heparin for venous thromboembolism prophylaxis, vitamin D and calcium supplementation, antihypertensive treatment with labetalol and amlodipine, insulin detemir for glycemic control, and Pneumocystis jirovecii pneumonia prophylaxis with trimethoprim-sulfamethoxazole due to severe hypercortisolism. Clinical and biochemical improvement was observed, with serum cortisol decreasing to 32 µg/dL, UFC to 530 µg/24h, and midnight salivary cortisol to 0.59 µg/dL.

A cesarean section was performed at 34+5 weeks of gestation, resulting in the delivery of an appropriate-for-gestational-age healthy neonate, who required cortisol supplementation for several months. Following delivery, all medications were discontinued, with normalization of cortisol levels and marked clinical improvement. An hCG stimulation test confirmed the diagnosis of PICS: following administration of 13,000 units of hCG, serum cortisol increased from 15.6 µg/dL at baseline to 34 µg/dL at 48 hours, ACTH decreased from 14.4 pg/mL to undetectable levels, and UFC increased from 28 µg/24h to 293 µg/24h. The patient elected conservative medical management in future pregnancies.

Conclusion:
PICS is a rare and diagnostically challenging cause of hypercortisolism during pregnancy. This case highlights successful medical management of severe PICS presenting in the second trimester, despite the absence of adrenal abnormalities on imaging. Early recognition, close biochemical monitoring, and comprehensive multidisciplinary care enabled favorable maternal and neonatal outcomes.

153

Assessment of Bone Mineral Density and Trabecular Bone Score in Adolescents and Young Adults With Primary Ovarian Insufficiency

Noah Gruber[1,2], Shai Bar-Shira[1,2], Myriam Safrai[2,3], Moran Shapira[2,3], Yael Levy-Shraga[1,2]
[1]*Pediatric Endocrine and Diabetes Division, Edmond and Lili Safra Children's Hospital, Sheba Medical Center*
[2]*The Gray Faculty of Medical and Health Sciences, Tel-Aviv University*
[3]*IVF unit, Department of Obstetrics and Gynecology, Sheba Medical Center*

Background:
Primary Ovarian Insufficiency (POI) in adolescents and young women is associated with reduced bone mineral density (BMD) and elevated fracture risk. While BMD reflects bone quantity, the trabecular bone score (TBS) offers complementary insights into bone quality. Data on bone health parameters in young females with POI, particularly comparing Turner syndrome (TS) and non-TS etiologies, remain scarce. We aimed to evaluate BMD and TBS in this population and assess the impact of hormone replacement therapy (HRT).

Methods:
We conducted a retrospective study of girls aged 10–24 years with POI who underwent dual-energy X-ray absorptiometry (DXA) at our center between 2020–2025. POI was defined as irregular menses and FSH 20 IU/L on two occasions. Lumbar spine BMD was assessed (GE Lunar Prodigy) and adjusted for size using bone mineral apparent density (BMAD). Trabecular bone microarchitecture was analyzed using TBS iNsight (Medimaps). Z-scores were calculated from age- and sex-specific reference data. Clinical and hormonal characteristics were retrieved from medical records and compared between TS and non-TS patients.

Results:
Twenty-eight girls (mean age 18.4 ± 3.7 years) underwent DXA. POI was diagnosed at a mean age of 13.9 ± 3.1 years, earlier in TS vs. non-TS (11.6 ± 1.6 vs. 15.4 ± 2.9 years, p = 0.001). At baseline, mean lumbar spine BMD Z-score was –1.50 ± 1.20, and TBLH Z-score –0.67 ± 0.81, both below normative values. TBS Z-scores were also reduced (–0.73 ± 0.8), and significantly lower in non-TS compared with TS (–1.01 ± 0.74 vs. –0.23 ± 0.70, p = 0.01). TS patients had longer HRT exposure before DXA (3.9 ± 3.1 vs. 0.3 ± 1.6 years, p = 0.03). In four girls with follow-up DXA, TBS Z-scores improved after ~2 years of HRT (–0.83 ± 0.8 to –0.32 ± 0.62, NS).

Conclusions:
Adolescents and young women with POI exhibit impaired bone mass and quality. Non-TS patients are particularly vulnerable, with lower BMD and TBS compared with TS, possibly reflecting shorter HRT exposure. These findings underscore the importance of early diagnosis and timely initiation of HRT to optimize bone health in girls with POI.

154

Intensive versus conventional hyperglycemic control in hospitalized non-critically ill patients, a multicenter, randomized control trial

Irit Ayalon-Dangur[1,2], Michal Michaelis[3], Irina Genin[4], Maya Arlyuk[4], Tzippy Shohat[5], Lichay Kaufman[4], Noam Shira Darnell[4], Tal Shapira[6], Leonard Leibovici[2,7], Yaron Rudman[1,2], Maly Keler[8], Ronit Koren[2,8], Jen Hojman[8], Mogher Khamaisi[9], Said Darawshi[9,10], Marco Bertolotti[11], Yonatan Shneor Patt[12], Ran Abuhasira[13,14], Idit F Liberty[14,15], Nuphar Vinegrad[14,15], David Fischer[14,15], Kim Ben Tikva Kagan[16], Alon Grossman[2,4]; [1]*Institute of Endocrinology, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel.* [2]*Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.*
[3]*Department of Internal Medicine E, Rabin Medical Center, Petah Tikva, Israel.*
[4]*Department of Internal Medicine B, Rabin Medical Center, Petah Tikva, Israel.*
[5]*Bio-statistical institute, Rabin Medical Center, Beilinson Campus, Israel.*
[6]*Department of Internal Medicine D, Rabin Medical Center, Petah Tikva, Israel.*
[7]*Research Authority, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel.*
[8]*Department of Internal Medicine A, Shamir Medical Center, Zerifin, Israel.*
[9]*Clalit health services, north district, Israel.*
[10]*Department of Internal Medicine D, Rambam Health Care Campus, Haifa, Israel.*
[11]*Department of Biomedical, Metabolic and Neural Sciences, Unit of Geriatric Medicine University of Modena and Reggio Emilia, University Hospital of Baggiovara, Modena, Italy.*
[12]*Department of Internal Medicine B, Sheba Medical Center, Tel-Hashomer, Israel.*
[13]*Clinical research center, Soroka University Medical Center, Beer-Sheva, Israel.*
[14]*Faculty of health sciences, Ben Gurion University of The Negev, Beer-Sheva, Israel.*
[15]*Diabetes Clinic, Soroka University Medical Center, Beer-Sheva, Israel.*
[16]*Department of Internal Medicine A, Rabin Medical Center, Petah Tikva, Israel.*

Objectives: The aim of the current study was to evaluate whether conventional is superior to intensive glucose control in hospitalized non-critically ill patients.

Methods: A multicenter, double blind (subject and assessor), randomized, prospective, superiority study to compare intensive vs. conventional glycemic control in hospitalized non-critically ill patients. Within 24 hours of admission, patients anticipated to require hospitalization for a minimum of three days were randomly assigned to either intensive glucose control (blood glucose target of 130 mg/dL or less) or conventional glucose control (blood glucose target of 131-180 mg/dL). The primary outcome was a composite of mortality, severe infections, stroke and cardiac ischemic events within 30 days and severe hypoglycemia within 90 days.

Results: A total of 406 patients were randomized between 2018 and 2025 across five centers. Of them 206 patients to the intensive group (mean age 70.3±10.7, 57.7% males) and 200 patients to the conservative group (mean age 69.7±10.4, 63.5% males). The primary outcome did not differ between the two groups, 35 events in the conservative (17.5%), and 26 events in the intensive (12.6%) group, P=0.18. Mortality rate within 90 days was similar between the two groups (20 patients died in the intensive group vs 18 patients in the conservative group, P=0.66). A total of 25 patients in the intensive, compared to 20 patients in the conservative group experienced a hypoglycemic event, P=0.57. The rate of severe hypoglycemic events (blood glucose level40 mg/dL) and duration of hospitalization did not differ between the two groups [one patient (0.5%) in the intensive vs three patients (1.5%) in the conservative group experienced severe hypoglycemic event, P=0.26. Median length of hospitalization was five days in both groups]. A per-protocol analysis limited to patients whose mean blood glucose levels were consistent with their allocation according to the study protocol was done, showing no difference from the intention to treat analysis, demonstrating no significant difference between the two study groups in all outcomes measured, except from a trend toward more hypoglycemic events in the intensive control group (P=0.06).

Conclusions: In this randomized controlled trial, intensive glucose control (blood glucose target of 130 md/dL or less) in hospitalized non critically ill patients did not result in any favorable outcome compared with conventional glucose control. (ClinicalTrials.gov number, NCT03510078).

familial hypogonadotropic hypogonadism linked to a novel pathogenic intronic variant in *FGFR1* gene

Michal Yacobi Bach[1,2], Alina Kurolap[1], Rona Hagin[1]
[1]*The Genetics Institute and Genomics Center, Tel Aviv Sourasky Medical Center*
[2]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Mediccal Center*

Introduction

Hypogonadotropic hypogonadism (HH) is a rare endocrine disorder that arises due to insufficient secretion of gonadotropin-releasing hormone (GnRH). More than 20 genes have been implicated in the pathogenesis of HH, particularly those involved in the development and migration of hypothalamic neurons and in GnRH signaling pathways. In this report, we describe a familial case of HH caused by a pathogenic intronic variant in the FGFR1 gene, which leads to abnormal gene splicing and subsequent gonadal dysfunction.

Case Description

The proband is a 53-year- woman who presented with primary amenorrhea, delayed sexual development, and anosmia. Hormonal evaluation was consistent with hypogonadotropic hypogonadism. She had previously received gonadotropin therapy for fertility treatment. A prior genetic panel did not identify any causative variants. Her three daughters exhibited delayed puberty and reproductive dysfunction, with variable severity.

Exome sequencing was performed on all affected family members and identified a novel intronic variant in the FGFR1 gene, c.92-19GA, located in intron 2. This variant was present in all symptomatic family members and was absent from both the gnomAD database and internal variant databases. Although previously classified as a variant of unknown significance (ClinVar: VCV000430230.3), the segregation of this variant with the clinical phenotype in this family supports its pathogenic role.

Methods

Exome sequencing (ES) was conducted on all affected family members. The sequencing was performed in-house using the Illumina NovaSeq 6000 sequencer and the IDT xGen Exome Research Panel v2 for library preparation. The bioinformatics pipeline and variant analysis were carried out using Franklin by Genoox data analysis software.

To determine the functional impact of this non-canonical intronic variant, RNA studies were conducted to evaluate splicing patterns and to identify any alterations in mRNA isoforms.

Results

SpliceAI analysis predicted that the variant disrupts the canonical splice acceptor site in exon 3, with a high confidence score of 0.97. RNA analysis from patient-derived peripheral blood mononuclear cells (PBMCs) confirmed aberrant splicing. Specifically, the G-to-A substitution resulted in the inclusion of 17 nucleotides from intron 2 into exon 3, causing a frameshift and introducing a premature stop codon.

Conclusion

This report describes a familial case of hypogonadotropic hypogonadism in a mother and her three daughters, caused by a novel pathogenic non-canonical splice-site variant in FGFR1. The findings highlight the critical role of non-coding regions in gene regulation and disease pathogenesis. This case contributes new insights into FGFR1-related HH and underscores the clinical significance of intronic variants in genetic diagnosis.

Social Physiology: Glucose Homeostasis Is More Efficient in Social Proximity

Shir Atzil[1], Monia Masalha[1], Matan Cohen[1], Maayan Aloni[1], Einav Toledo[1], Ella Stahl[1], Diane Shachar[1], Or Eliav[1], Shai Fuchs[2]

[1]*Department of Psychology, The Hebrew University of Jerusalem*

[2]*Paediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel*

Physiological homeostasis is classically defined as a process maintained within the individual, where adaptations enhancing homeostatic efficiency are under intense positive selection. However, this individual-centric framework has obscured the possibility that in social animals, sociality may itself be conserved because it sustains homeostatic efficiency. In this talk, I apply a neuroscience-evolutionary framework to test the hypothesis that in social animals such as humans, social bonds serve a fundamental role in managing homeostasis itself. While previous research has recognized the evolutionary role of sociality through behavioral and ecological support in cooperation or threat, no research has tested whether social proximity enhances core homeostatic regulation in systems not traditionally viewed as socially sensitive, such as glucose metabolism.

In a set of preregistered experiments, we found that glucose homeostasis following a carbohydrate challenge is more efficient, exhibiting lower perturbation amplitude and faster recovery in the Social condition compared to Alone (n=108). We replicated this pattern in thermoregulation during cold challenge (n=116) and in sympathetic regulation during stress in adults (n=115) and infants (n=58). Across systems, social proximity reduced perturbation magnitude and accelerated recovery, independent of stress reduction or touch.

These findings demonstrate ***Social Physiology***: a cross-domain principle in which core homeostatic processes operate more efficiently in social proximity. The consistent reduction in plasma glucose in social contexts suggests that social information may be a meaningful predictor, and potentially a mechanistic contributor, to glucose homeostasis, with implications for glucose testing and management.

157

The GAPP Aggressivity Score Correlates with Somatic Non-Missense Mutation Burden in Pheochromocytoma

Reut Halperin[1,2], Gil Goldinger[3], Eddie Fridman[3], Naama Peshes Yaloz[1], Amit Tirsoh[1,2], Gadi Shlomai[2,4]

[1]*ENTIRE - Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba MC*

[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

[3]*Pathology, Sheba MC*

[4]*Division of Endocrinology, Diabetes and Metabolism, Sheba MC*

Pheochromocytomas and paragangliomas (PPGLs) can show metastatic potential in up to 30% of cases. To assess the risk of aggressive behavior, histopathological scoring systems like the PASS and GAPP have been developed. However, it remains unclear whether the severity indicated by these scores corresponds to genetic alterations.

Methods

A retrospective pilot study including twenty patients with pheochromocytoma. Patients were stratified into high- and low-risk groups based on GAPP and PASS scores. Tumor mutation burden (TMB), derived from whole-exome sequencing, and clinical variables were compared between groups.

Results

Six patients (30.0%) comprised the high-risk group; all had PASS scores 4 and GAPP scores indicating moderately differentiated PPGLs. Compared with the low-risk group, the high-risk group had larger tumors (4.7 vs. 3.4 cm, $p = 0.03$) and showed trends toward higher diastolic blood pressure (90 vs. 79 mmHg, $p = 0.09$), normetanephrine (8.5 vs. 2.3 X upper limit of normal [ULN], $p = 0.08$), and metanephrine (22.9 vs. 9.25 X ULN, $p = 0.09$) levels. The high-risk group demonstrated a higher TMB, particularly for non-missense variants (32 vs. 26, $p = 0.04$). As a continuous variable, only the GAPP score, not PASS score, showed a significant positive correlation with TMB, observed for both non-missense ($r = 0.57$, $p = 0.009$) and frameshift ($r = 0.47$, $p = 0.04$) variants.

Conclusions

Higher pathological severity scores are associated with increased rates of severe molecular somatic variants. The stronger link between the GAPP score and genetic alteration rates suggests that it more accurately reflects the genomic complexity of PPGLs.

158

Family history predicts primary hyperparathyroidism regardless of genetic predisposition

Reut Halperin[1,2], Liana Tripto-Shkolnik[2,3], Iris Vered[3], Pinchas Klein[2,3], Galit Avior[2,4], Hadar Miloh-Raz[2,3], Jacob Ilani[3], Naama Peltz-Sinvani[2,3], Tali Cukierman-Yaffe[2,3], Nir Lasman[2,3], Sigal Ben-Shmuel[3], Amna Jabarin[2,3], Yehudit Eden-Friedman[2,3], Gil Goldinger[2,5], Gadi Shlomai[2,3], Naama Pashes-Yaloz[1,2], Amit Tirosh[1,2]

[1]*ENTIRE - Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba MC*

[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

[3]*Division of Endocrinology, Diabetes and Metabolism, Sheba MC*

[4]*Department of Otolaryngology-Head and Neck Surgery, Sheba MC*

[5]*Pathology, Sheba MC*

Primary hyperparathyroidism (PHPT) has a known genetic predisposition in only 10% of cases. We aimed to identify predictors of PHPT occurrence in carriers and non-carriers of a pathogenic variant (PV) in PHPT-related genes.

Methods

A prospective study of patients who underwent genetic assessment for PHPT or suspected endocrine neoplasia syndrome. Demographics, clinical, biochemical, and genetic findings were compared between patients with and without PHPT.

Results

Overall, 249 patients were included, 34.5% with PHPT. Sixty-five (26.1%) carried PV in PHPT-related genes, mainly the GCM2 p.Y394S PV (7%) and MEN1 (4%). PV rate in patients with PHPT was 37% (MEN1 13%, GCM2 p.Y394S 8%). Patients with PHPT and a family history (FH) of PHPT had higher PV risk than those without FH (73.7% vs 26.9% p=0.001), were younger at diagnosis (37.1±15.2 vs 50.0±18.3, p=0.006), had a higher risk of recurrence (21.1% vs 1.7% p0.001), and of PHTP-related target organ damage (p0.006). MEN1 and GCM2 PVs carriers had more glands involved vs non-carriers (MEN1: 2.4±1.82 vs 0.94±0.25, p=0.004; GCM2: 2.00±1.00 vs 0.94±0.25, p=0.001). GCM2 PV carriers had a wide clinical spectrum, from no PHPT (58%), mild PHPT, to hypercalcemic crisis at a young age. In multivariable analysis, FH predicted PHPT occurrence (OR 39.22, 95% CI 4.9-5074.7, p0.0001) independently of PV carrier status.

Conclusions

Family history is a significant predictor of primary hyperparathyroidism (PHPT), even if genetic testing does not reveal any findings. This suggests the presence of unrecognized genetic or epigenetic factors. The GCM2 p.Y394S variant is relatively common and presents with variable phenotypes, highlighting its importance in the genetic evaluation of patients with PHPT

159

Earlier Menopause and Risk of Metabolic Dysfunction-Associated Steatotic Liver Disease: A Global Cohort Study

Joshua Stokar[1], Rivka Dresner-Pollak[1]
Endocrinology, Hadassah Hebrew University Medical Center

Objectives

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing public health concern, contributing to liver and cardiovascular complications. Prevalence of MASLD in women increases sharply around age 50 years, but the relationship between an earlier age at natural menopause and MASLD is unknown.

Methods

Using the TriNetX global federated network, we identified women with earlier menopause (50y). The control cohort consisted of similarly aged pre-menopausal women. Cases of premature (40y) or surgical menopause, non-MASLD causes of steatotic-liver disease (SLD), or sex-hormone therapy were excluded. Propensity-score matching adjusted for baseline characteristics and metabolic risk factors, resulting in two matched cohorts of 20,979 women (total n = 41,958) in the final analysis. Outcomes included new diagnoses of MASLD (metabolic dysfunction-associated steatohepatitis) and the MASLD metabolic factors: pre-diabetes/diabetes, hypertension, dyslipidemia, and overweight/obesity over 5-years of follow-up.

Results

Earlier menopause was associated with an increased risk of developing MASLD (HR 1.322, 95%CI 1.170-1.492), new onset dyslipidemia (1.083; 1.045-1.122) and pre-diabetes (1.130; 1.060-1.205). Findings were consistent across stratified analyses by preexisting metabolic risk-factors (HR 95%CI for MASLD with preexisting dysglycemia 1.370, 1.042-1.800; dyslipidemia 1.340, 1.053-1.705; hypertension 1.230, 0.998-1.516; overweight 1.280, 1.086-1.510).

Conclusions

Risk for MASLD is increased following menopause before age 50. Further studies should assess incorporation of menopause timing into female-specific cardiometabolic risk assessment.

161

IL-1β modulates glucagon- and cortisol-driven hepatic transcriptional programs

Talia Frishman[1], Ido Goldstein[1]
Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem

Hepatic gene expression is tightly controlled by metabolic hormones that coordinate energy balance. Glucagon and cortisol activate transcriptional programs that promote energy mobilization during fasting, circadian transitions, and immune activation, whereas insulin is classically viewed as the dominant postprandial antagonist of these programs. Il-1β is classically considered a principal inflammatory signal mediating its effects by phosphorylation cascades and NF-κB activation. Emerging evidence, indicates that, similarly to insulin, IL-1β levels rise following feeding. This suggest interaction between IL-1β and metabolic hormones – glucagon and cortisol. How IL-1β influences glucagon- and cortisol-driven hepatic gene regulation has not been systematically examined.

Here, we employed genome-wide RNA-seq and ChIP-seq approaches to investigate how IL-1β modulates hepatic transcriptional responses to metabolic hormones. Our analyses reveal extensive bidirectional crosstalk between IL-1β and glucagon- and cortisol-mediated signaling. IL-1β antagonizes glucagon- and cortisol-induced metabolic gene programs, while simultaneously synergizing with these hormones to promote immune-related gene expression programs. These opposing effects are organized into distinct transcriptional clusters, underscoring the context-dependent nature of IL-1β signaling in hepatocytes.

At the mechanistic level, these transcriptional responses are accompanied by dynamic changes in transcription factors chromatin binding. IL-1β reduces glucocorticoid receptor (GR) occupancy at a subset of genomic sites, while cooperative chromatin binding involving NF-κB is observed at others. Importantly, extensive analyses revealed no evidence that these effects arise from impaired upstream glucagon or cortisol signaling. Instead, IL-1β transcriptional response requires NF-κB activity, showing that NF-κB mediates the antagonistic and synergistic effects of IL-1β on hormone-driven transcription.

Notably, these transcriptional and chromatin-level changes translate into a functional metabolic phenotype. IL-1β suppresses hepatic glucose production in primary hepatocytes, whereas inhibition of NF-κB abolishes this effect. Together, these findings demonstrate that IL-1β modulates hepatic hormone responses through NF-κB-dependent transcriptional and chromatin-based mechanisms, extending its role beyond classical inflammatory signaling to the regulation of hepatic metabolic function.

A deflection point during weight loss: Call for identification and action

Brurya Tal[1], Gabi Shefer[1], Jessica Sack[1], Yonit Marcus[1], Yael Sofer[1], Marianna Yaron[1], Limor Ben Haim[1], Yona Greenman[1], Naftali Stern[1]

The Sagol Center for the Metabolic Syndrome, Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center; Sackler Faculty of Medicine, Tel Aviv University, Israel

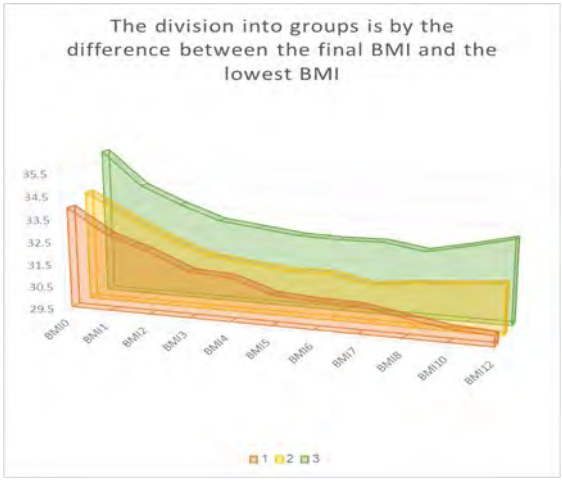
Background: This study investigates whether a high-protein Mediterranean diet can enhance metabolic health. Protein-rich foods are known to boost satiety, preserve lean body mass, improve glycemic control, and reduce visceral fat—key markers of metabolic syndrome. Persistence in adhering to such a diet is hypothesized as critical to achieving these benefits.

Methods: Seventy-two participants (40 men, 32 women; mean age 57.65±12.16) diagnosed with metabolic syndrome according to ATPIII criteria, underwent a one-year intensive multidisciplinary intervention, including personalized physical training and a high-protein Mediterranean diet.

Results: A weight loss curve was generated individually and classified at the end of the year according to weight loss trends Three weight loss patterns were observed: Group A (N=31) continued to lose weight throughout the study, reaching a 12% reduction; Group B (N=22) showed a steep initial decline, but regained between 0.3 and 0.8 BMI units from the nadir weight, with a mean deflection point average of 7 months, translating into a mere 6% eventual weight loss; and Group C (N=19) started to lose rapidly at the onset, but showed thereafter a larger regaining of weight (0.9 and 3 BMI units) from the lowest attained weight, with a final overall weight loss of 8%. The initial BMI did not differ significantly among groups.

Weight loss was significant (p0.0001) in all groups. Expectedly, Group A, with the best weight loss, demonstrating superior metabolic improvements, manifested by greater reductions in fat mass (p=0.02), triglycerides (p=0.02), diastolic blood pressure (p=0.04), heart rate (p=0.006), and sugar intake (p=0.03), had a weight loss outcome (p0.0001) by the end of the year. Segregation into groups A, B, and C could not be predicted by age, initial BMI or sex. Deflection points for weight regain averaged at 7-8 months, but treatment was not modified at this point.

Conclusion: Even under a tightly structured, personnel-rich multidisciplinary weight loss program, weight regain or at least stagnation occurs after initial weight loss in nearly 60% of the patients. We believe that timely identification of deflection from weight loss, the deflection time, should be identified and explored individually for adherence to the prescribed program. Furthermore, the biological basis of the deflection point in terms of biological mechanisms is worthy of direct further research. Whether the identification of a deflection point can be utilized to enhance the outcome remains to be studied.



163

Moderate Carbohydrate Reduction Is Not Associated with Maternal Ketosis or Adverse Pregnancy Outcomes in Insulin-Treated Pregnancy: Interim Safety Data from a Randomized Controlled Trial

Naama Shirazi[1,2], Danny Ben-Zvi[1,2], Yoel Toledano[3], Einat Mazor[3], Meital Ron-El[3], Sarit Hellman[4], Maayan Bas Lando[2,4], Karen Hershkop[4], Gil Leibowitz[1,2], Genya Aharon-Hananel[1,2]

[1]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel.*

[2]*Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*

[3]*Division of Maternal Fetal Medicine, Helen Schneider Hospital for Women*

[4]*Medical Center, Petah Tikva, Israel⁴ Shaare Zedek Medical Center, Jerusalem, Israel*

Background: Uncontrolled diabetes during pregnancy increases maternal and fetal morbidity. Pregnancies requiring intensive insulin therapy (IIT), safe nutritional strategies are essential for optimal glycemic control. Current guidelines recommend a minimum carbohydrate intake of 175 g/day for all pregnant women, including IIT, despite limited supporting evidence. Moderate carbohydrate reduction may improve glycemia, but concerns remain regarding maternal ketosis, fetal growth, and hypoglycemia.

Objective: To present interim safety findings from an ongoing randomized controlled trial (RCT) evaluating moderate carbohydrate reduction in pregnant women on IIT.

Methods: This multicenter RCT aims to enroll 120 pregnant women with diabetes (type 1/2/MODY/GDM) requiring IIT. Participants are randomized to either a moderate carbohydrate reduction diet (120 g/day) or standard dietary care (minimum 175 g/day), with structured counseling every two weeks in a multidisciplinary high-risk pregnancy-clinic.

Safety monitoring includes predefined maternal and fetal endpoints: maternal ketosis, fetal growth, preterm delivery (

Interim Safety Findings:To date, 55 of 120 participants have been enrolled, 32 have delivered across three centers (standard care n = 19; intervention n = 13). No episodes of clinically significant maternal ketosis were observed. All fasting β-hydroxybutyrate values were

Fetal growth trajectories were within expected ranges. At the final clinic visit prior to delivery (≈36 weeks' gestation), mean estimated fetal weight was similar between groups (3095 g in the intervention group vs. 3086 g in standard care), corresponding to approximately the 75th percentile for gestational age. Mean abdominal circumference was also comparable (343 mm vs. 340 mm), corresponding to the 80th percentile. Amniotic fluid volume was normal in all participants in the intervention group, with a single case of polyhydramnios observed in the standard care group.

Limitation: Interim findings are based on a partial sample size, and rare adverse outcomes may not yet be fully captured.

Conclusions: Interim data-analysis reveals no safety signal associated with moderate carbohydrate reduction in insulin-treated pregnancy, supporting continued evaluation of evidence-based dietary recommendations in this population.

164

Real-World Teplizumab in Stage 2 Type 1 Diabetes: Safety Signals, Laboratory Kinetics, and Early Glycemic Outcomes in an Eight-Patient Case Series

Nir Lasman[1], Yair Schwarz[1]
Division of Endocrinology, Diabetes & Metabolism, Sheba Medical Center

Background: Teplizumab (a humanized anti-CD3 monoclonal antibody) can delay progression from stage 2 to stage 3 type 1 diabetes (T1D), but real-world safety patterns and short-term laboratory dynamics during treatment remain clinically important, particularly in adult practice settings. We report our center's experience with teplizumab in patients with stage 2 T1D, focusing on temporal trends in lymphocyte counts, inflammatory markers, hepatic enzymes, and infusion-associated reactions, alongside early glycemic outcomes.

Methods: We conducted a descriptive case series of eight patients with stage 2 T1D treated with a 14-day course of teplizumab per institutional protocol. Clinical monitoring included daily assessment for hypersensitivity symptoms and serial laboratory evaluation, with particular attention to absolute lymphocyte count (ALC), C-reactive protein (CRP), and liver function tests. Supportive medications were administered daily during treatment, including an antihistamine and ibuprofen, as part of reaction mitigation.

Results: All patients demonstrated a reproducible on-treatment hematologic pattern, with ALC reaching a nadir consistently around day 5 of therapy, followed by recovery thereafter. CRP rose transiently with a peak occurring in a similar mid-course window, consistent with a self-limited inflammatory response. Several patients exhibited mild, transient elevations in hepatic transaminases during treatment; these abnormalities resolved without reported progression to clinically significant liver injury. Mild hypersensitivity-type reactions occurred in a subset of patients, including rash and transient swelling of the face and fingers; symptoms resolved with supportive care and did not preclude completion of the 14-day course.

Regarding glycemic outcomes, progression to stage 3 disease was heterogeneous: some patients initiated insulin after completing therapy, whereas others remain insulin-independent at last follow-up, suggesting variable trajectories despite a shared early immunologic/laboratory response pattern.

Conclusions: In this eight-patient real-world series of stage 2 T1D treated with teplizumab, we observed consistent mid-treatment lymphocyte nadir (day ~5) and parallel transient CRP elevation, with generally mild, self-limited adverse events including occasional transient transaminitis and mild hypersensitivity reactions. Early post-treatment glycemic outcomes were mixed, with ongoing insulin-free status in some patients. Larger prospective real-world cohorts with standardized follow-up are needed to clarify predictors of insulin-free survival and to refine monitoring strategies during treatment.

166

Triglyceride-Glucose Index and Risk of End-Stage Liver Disease in Young Adults: A Nationwide Cohort Study

Michal Kasher Meron[1,2], Tzipi Hornik-Lurie[3], Pnina Rotman-Pikielny[1,2], Gilad Twig[2,4], Tomas Karpati[5]

[1]*Endocrinology, Meir Medical Center*

[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

[3]*Research, Meir Medical Center*

[4]*Endocrinology, Sheba Medical Center*

[5]*Faculty of Sciences and Department of Digital Medical Technologies, Holon Institute of Technology*

Objectives: Insulin resistance is strongly associated with metabolic dysfunction-associated steatotic liver disease (MASLD), yet both remain underdiagnosed in young adults. The triglyceride-glucose (TYG) index has been proposed as a predictor of incident diabetes, MASLD, and cardiovascular events. We assessed whether TYG index predicts incident end-stage liver disease in young adults.

Methods: This retrospective cohort study used a nationwide database including adults aged 18–40 years with TYG index calculated during 2005–2020. We excluded individuals with diabetes, chronic liver disease other than MASLD or those treated with anti-diabetic or lipid lowering medications. TYG was categorized into quartiles defined separately for men and women to account for sex-specific distributions. The primary outcome was first diagnosis of cirrhosis, cirrhosis-related complications, or hepatocellular carcinoma. Cox proportional hazards models assessed associations adjusted for age, sex, ethnicity, BMI.

Results: Among 725,486 participants (median follow-up 12.5 years), 286 incident end-stage liver disease cases occurred (3.46 per 100,000 person-years; mean age at diagnosis 30.3 ± 5.3 years). TYG index increased with age in both sexes, with women showing consistently lower values, reflecting distinct sex-specific distributions. Higher TYG quartiles showed increased risk in unadjusted analysis (Q4 vs Q1 HR: 1.62, 95% CI: 1.18-2.21). However, after adjusting for age, sex, ethnicity and BMI the association was no longer significant (adjusted HR: 1.15, 95% CI: 0.82-1.61).

Conclusions: Established metabolic risk factors account for the association between TYG index and end-stage liver disease in young adults. TYG does not provide added value beyond conventional metabolic parameters for liver disease risk stratification in this population.

167

Effect of hyperbaric oxygen therapy in youth with newly diagnosed type 1 diabetes: a randomized controlled proof-of-concept trial

Avigail Wittenberg[1,2], Dana Arad[1,3], Sharon Shtrausman[4], Orit Pinhas-Hamiel[5,6], Shai Efrati[6,7], **Marianna Rachmiel**[1,6]

[1]*Pediatric Endocrinology and Diabetes Institute, Shamir (Assaf Haroffeh) Medical Center*

[2]*Department of Pediatrics, Division of Endocrinology, University of British Columbia, Vancouver, BC, Canada.*

[3]*Koret school of Veterinary Medicine, Hebrew University of Jerusalem*

[4]*Pediatric Endocrine Unit, Kaplan Medical Center, Rehovot , Israel*

[5]*Pediatric Endocrine and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Ramat-Gan, Israel*

[6]*Gray School of Medicine, Tel Aviv University , Tel Aviv, Israel*

[7]*Sagol Center for Hyperbaric Medicine and Research, Shamir (Assaf Haroffeh) Medical Center*

Background: Type 1 diabetes (T1D) is an autoimmune disease marked by autoimmune pancreatic β-cell destruction. Hyperbaric oxygen therapy (HBOT) has been shown to have anti-inflammatory and regenerative effects in animal models and autoimmune disorders.

Aim: To assess the effects of HBOT on immune parameters and β-cell function in children and adolescents with new-onset T1D.

Methods: In this proof-of-concept randomized 2:1 controlled trial, participants aged 8–19 years, diagnosed within 90 days of T1D onset, and with measurable C-peptide levels, received standard insulin therapy alone or combined with 60 HBOT sessions (100% oxygen at 2 ATA for 90 minutes) over 12 weeks. β-cell function, glycemic control, and immune parameters (Treg-$CD4^+$ cells, serum cytokines, and PBMC-secreted cytokines) were measured at baseline, 12, and 24 weeks.

Results: Of 23 participants, 8 withdrew. Comparison between the HBOT group (n=9; 33.3% male; median age 10.5 years) and controls (n=6; 66.7% male; median age 12.75 years) showed minimal statistically significant differences. At 12 weeks, time-in-range (70–180 mg/dL) remained stable with HBOT but declined in controls (p=0.03). CTLA-4^+ Tregs were lower at 12 weeks in the HBOT group (p=0.05) and PBMC counts were lower at 24 weeks (p=0.05). Serum IL-12 levels increased at 12 weeks in HBOT group (p=0.03), suggesting enhanced Th1 immune activity, while PBMC IL-8 production rose (p=0.01), including a significant delta between visits (p = 0.03), indicating possible tissue repair and vascular remodeling.

Conclusions: HBOT was well tolerated and induced modest immune modulation with preserved glycemic stability in early T1D. Larger, longer-term trials are warranted to confirm these findings.

Close Access to Health Care as a Bridge Overcoming Disparities in Thyroid Cancer

Oded Cohen[1,2], Larisa Aizikovich[2], Uri Yoel[2,3], Merav Frenkel[2,3], Liroy Kalakuli[2]
[1]*Otolaryngology, Head and Neck Surgery, Assuta Samson Ashdod*
[2]*Ben Gurion University*
[3]*Endocrinology, Soroka Medical Center*

Introduction: Studies occasionally demonstrate various ethnic disparities regarding differentiated thyroid cancer (DTC) characteristics and outcomes. The impact of public health care and close access to care has been studied scarcely. With a unique minority group within the hospital region, this case control study aims to investigate this further.

Methods: A retrospective cohort study of patients with DTC diagnosis who followed-up at a tertiary medical center between 2013 and 2024. The patients were categorized into Minority (study group) or non-minority (control group) and were reviewed for DTC characteristics at presentation and outcomes including histopathology, risk of structural disease recurrence, response to initial treatment, and mortality and risk group according to the ATA guidelines.

Results: A total of 237 patients were included, of whom 84 (32%) constituted the minority group. 173 (73%) were females. The minority group was diagnosed at a younger age compared to non-minority group (42 ± 15 vs. 54 ± 16 years, p0.001) and had higher rates of female patients (82% vs. 68%, p=0.019, respectively). The median follow-up of the cohort was 4.70 (2.36-7.65) years. DTC characteristics did not demonstrate significant differences regarding size distribution, multifocality, LN or distant metastasis. However, the minority group had lower rates of ETE (24% vs. 40%, p=0.032). The extent of surgery, ATA risk classification, response to initial therapy, and the need for additional intervention were comparable between the groups. During the study period, 19 (8%) patients died, including 6 (2.5%) disease-specific deaths, with no between-group differences in all-cause or disease-specific mortality.

Conclusions: Our findings suggest that a good access to non-insurance based, public healthcare may reduce thyroid cancer disparities, which was reported repeatedly up to date. Health system structure and language barriers may play a role in disparities attributed to ethnicity.

170

Cardiovascular safety of Romosozumab therapy in men with osteoporosis

Hadar Duskin-Bitan[1,2], Doron Netzer[3,4], Lilach Dolev[3], Arnon D Cohen[5,6], Doron Comaneshter[7]

[1]*Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center, Beilinson Hospital*

[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

[3]*Division of Community Medical Services, Clalit Health Services*

[4]*Adelson School of Medicine, Ariel University*

[5]*Department of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services*

[6]*Siaal Research Center for Family Medicine and Primary Care, Division of Community Health, Faculty of Health Sciences, Ben-Gurion University*

[7]*Department of Quality Measurements and Research, Clalit Health Services*

Aims: Romosozumab is an osteo-anabolic treatment for patients with severe osteoporosis. A signal for increased cardiovascular risk was observed in patients receiving romosozumab, especially in men patients. Real-world safety data in men is currently limited.

The aim of our study was to evaluate the cardiovascular risk in patients treated with romosozumab compared to teriparatide in men and women.

Methods: A retrospective cohort study using Clalit Health Services database, to assess the incidence of major adverse cardiovascular events (MACE) in patients with severe osteoporosis using osteo-anabolic medications.

Results: The cohort included 6,063 patients: 1,794 patients received romosozumab (66, 3.7% man), and 4,269 patients received teriparatide (404, 9.5% man). In the romosozumab group, the mean age was 73 and 73 for women and men, respectively. In the teriparatide group, the mean age was 71 and 74 for women and men, respectively.

At baseline, men in both the romosozumab and teriparatide cohorts had higher proportions of smoking compared to women (26% and 19% vs. 13% and 14%, p0.001), ischemic heart disease (IHD, 26% and 32% vs. 7% and 13%, p0.001), and congestive heart failure (CHF, 11% and 9% vs. 3% and 5%, p0.001) respectively. In the teriparatide group, men had significantly higher proportions of diabetes mellitus (DM) and cerebrovascular accidents (CVA). BMI was lower in men compared to women treated with romosozumab.

During the follow up period, we observed an increased risk for IHD CHF and CVA in men treated with romosozumab compared to other patients groups. Men patients treated with romosozumab had higher risk for hospitalization and death compered to women treated with romosozumab.

In a multivariate analysis, adjusted for age, obesity, DM, hypertension, dyslipidemia, renal function, smoking, recent steroid use, and previous bisphosphonates treatment, we observed an increased hazard ratio for IHD (2.2, 95%CI 1.5-3.3), hospitalization in cardiovascular departments (1.6, 95%CI 1.1-2.3) and death (1.4 95% 1-1.9) in men versus women, treated with romosozumab compared to teriparatide.

Conclusion: We observed an increased risk for IHD and death in men versus women, treated by romosozumab compared to teriparatide.

171

High Preoperative IGF-1 Levels in Cushing Disease: Prevalence and Postoperative Course

Merav Serebro[1], Karen Tordjman[1,2], Eugene Feigin[1,2], Lior Gonen[3], Yona Greenman[1,2]
[1]*Institute of Endocrinology, Diabetes, Hypertension and Metabolism, Tel Aviv-Sourasky Medical Center, Tel-Aviv, Israel.*
[2]*. Gray Faculty of Medicine, Tel Aviv University*
[3]*Department of Neurosurgery, Tel Aviv-Sourasky Medical Center, Tel-Aviv, Israel.*

Background

Elevated insulin-like growth factor 1 (IGF-1) levels, typically a marker of growth hormone (GH) activity, have been observed in some patients with Cushing disease, despite no clinical or biochemical evidence of GH excess. The significance and mechanism of this phenomenon remain unclear.

Study Population & Methods

A retrospective study of 78 patients with confirmed Cushing disease who underwent transsphenoidal surgery at Tel Aviv Sourasky Medical Center between 2007 and 2024. 48 patients with available preoperative IGF-1 data and postoperative endocrine follow-up were included in the study.

Results

Among 48 patients, 10 (20.8%) had elevated preoperative IGF-1 levels. OGTT was performed in three of these patients, all showing adequate GH suppression (0.4 ng/mL). No significant differences were found between patients with elevated vs. normal IGF-1 levels regarding demographics, comorbidities, or biochemical markers of hypercortisolism. Tumor characteristics (size, granulation pattern, Ki-67 index, ACTH immune reactivity, TPIT expression) and surgical outcomes (remission, reoperation, steroid dependency, or pituitary deficiencies) were also similar. Of the 10 patients with elevated IGF-1, four achieved remission; three of these (75%) showed IGF-1 normalization, with long-term data unavailable for one patient. Among six patients not in remission, five (83.3%) maintained elevated IGF-1 levels at follow-up, while one patient had normalized IGF-1 despite active disease.

Conclusions

Elevated IGF-1 levels occurred in a subset of patients with Cushing disease without evidence of GH excess, suggesting a non-GH-mediated mechanism. This phenomenon was not associated with distinct clinical, biochemical, or pathological features. Most patients who achieved remission demonstrated IGF-1 normalization. Further research is needed to clarify the pathophysiological and clinical relevance of this finding.

172

Ectopic ACTH Syndrome: A National Multicenter Experience Highlighting Early Mortality and Diagnostic Challenges

Merav Serebro[1], Orly Arias Gutman[1], Gadi Shlomai[2,3], Anat Bel-Ange[4], Simona Grozinsky Glasberg[4,5], Avraham Ishay[6,7], Irit Ayalon-Dangur[3,8], Ilan Shimon[3,8], Merav Fraenkel[9], Yona Greenman[1,3]

[1]*Institute of Endocrinology, Diabetes, Hypertension and Metabolism, Tel Aviv Sourasky Medical Center*

[2]*Institute of Endocrinology, Diabetes and Metabolism, Sheba Medical Center*

[3]*Gray Faculty of Medicine, Tel Aviv University*

[4]*Neuroendocrine Tumor Unit, Hadassah Medical Center*

[5]*Faculty of Medicine, Hebrew University of Jerusalem*

[6]*Endocrinology and Diabetes Unit, Haemek Medical Center*

[7]*Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology*

[8]*Institute of Endocrinology, Rabin Medical Center, Beilinson Campus*

[9]*Endocrinology Unit, Soroka University Medical Center*

Background: Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) presents a formidable challenge in endocrinology. It is characterized by the pathological secretion of ACTH from non-pituitary sources leading to a state of debilitating hypercortisolism. The purpose of this study was to report clinical presentation, tumor etiologies, diagnostic practices, therapeutic strategies, and short-term outcomes in a national multicenter cohort of patients with EAS.

Methods: Retrospective study across six tertiary centers in Israel, coordinated by Tel Aviv Sourasky Medical Center. Data was collected during 2014–2024. Outcomes included disease extent, biochemical burden, diagnostic utilization, treatment patterns, and survival.

Results: 32 adults were identified (median age 60.5 years; 53.1% men). Two-third were diagnosed during hospitalization, often due to edema or hypokalemia. Pulmonary sources predominated. At presentation, 58.1% had metastatic disease. Biochemical burden was substantial (median UFC ≈1,156 µg/24 h, ~15.4× ULN; ACTH ≈184 pg/mL, ~ 4.0× ULN). Hypokalemia was observed in 75.9% of patients, while diabetes and hypertension were present in 75.8% and 41.9%, respectively. Dynamic testing was performed in a minority of patients: CRH stimulation in 3.1%, 8-mg dexamethasone suppression in 25.0%, and inferior petrosal sinus sampling in 12.5%. Pituitary MRI was performed in 19 patients, and was negative in 89.5% of them. PET/CT was performed in 20 patients using 18F-FDG (n=14) and somatostatin receptor tracers (n=6), with an overall positivity rate of 50.0%. Treatment modalities included ketoconazole (67.7%) and/or metyrapone (64.2%) (often combined 42.8%), somatostatin receptor ligands (20.6%), chemotherapy (43%), bilateral adrenalectomy (12.9%) and primary tumor resection (37.5%). Among 32 patients, 17 (53.1%) died during follow-up, with a strikingly poor prognosis: median survival was only 42 days from diagnosis, with 30.8% dying within the first month, 61.5% within two months, and 76.9% within six months.

Infection-related complications, predominantly sepsis and opportunistic infections, were the leading cause of death (35.3%), reflecting the severe immunosuppression characteristic of hypercortisolism in ectopic Cushing`s syndrome.

Conclusions: In this national cohort, EAS was usually diagnosed at an advanced stage, characterized by acute clinical presentation, severe biochemical toxicity and high early mortality. These findings underscore the need for accelerated diagnostic pathways, rapid biochemical control, and streamlined multidisciplinary management.

175

Adipose tissue-derived FABP4 promotes melanoma growth by regulating the tumor microenvironment lipidomic landscape

Reem Igbaria[1,2], Rinat Livne[1], Amir Tirosh[1,2]
[1]*The Dalia and David Arabov Endocrinology and Diabetes Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center*
[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

There is a growing role for the adipose tissue in providing stromal support for tumor growth. In many cancers, peritumoral adipose tissue supports the growing tumor by various secreted factors including cytokines, adipokines, exosomes and lipids which are essential elements for energy, signal transductions and new membrane building.

Fatty acid binding protein 4 (FABP4) is a lipid chaperon with key roles in metabolic regulation, expressed in mature adipocytes, endothelial cells, macrophages, and dendritic cells. Accumulating evidence suggest that FABP4 may facilitate cancer growth, representing a potential mediator of adipose tissue-cancer crosstalk.

Melanoma, one of the cancers that develop adjacent to the subcutaneous adipose tissue, can be affected from the adipose-derived factors. The adipocytes-melanoma crosstalk supports the growth of primary melanoma, tumor invasion, angiogenesis, proliferation and metastasis.

In this study we generated B16-F10 melanoma spheroids (3-dimensional cell aggregates that recapitulate the *in-vivo* growth of cancers and better mimic the physiological complexity of the tissue) and treated them with conditioned media of either wild type (aCM^{WT}) or $Fabp4^{-/-}$ ($aCM^{Fabp4-/-}$) adipocytes. We observed that aCM^{WT} treated spheroids demonstrate a significant increase in spheroid area compared to $aCM^{Fabp4-/-}$. In addition, spheroids cultured with aCM^{WT} upregulated the cancer cell protein expression of FABP4 compared to spheroids treated with $aCMFabp4^{-/-}$. Furthermore, an increase in dead cells (Ethd-1 staining) was observed in spheroids cultured with $aCM^{Fabp4-/-}$ compared to aCM^{WT}. CM lipidomic analysis establishes enrichment of monounsaturated fatty acids (MUFAs) such as FA(14:1), FA(16:1) and FA(18:1) in $aCM^{Fabp4-/-}$. FA(14:1) and FA(18:1) are known apoptosis inducers in different cells. Spheroids lipidomic analysis showed elevated levels of several phospholipids in aCM^{WT} treated spheroids compared to $aCM^{Fabp4-/-}$ treated spheroids, including phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylinositol (PI) which are the main cell membrane building blocks, likely indicating increased cells division rate. In summary, the results of the current study highlight the importance of adipocytes-FABP4 in promoting melanoma progression, likely by providing crucial lipid products for the rapidly dividing cells and by scavenging deleterious lipid products. In addition, adipose tissue derived FABP4 stimulates the ectopic expression of this important lipid chaperon in the cancer cell thus promoting efficient lipid metabolism.

176

Multicomponent Lateralization Index to Enhance the Accuracy of Adrenal Venous Sampling (AVS) in Primary Aldosteronism Subtyping

yonit marcus[1], Gabi Shefer[2], Isaack Kori[3], Merav Ingbir[4], Yona Greenman[2], Naftali Stern[5]
[1]*Institute of Endocrinology, Metabolism and Hypertension, C*
[2]*Institute of Endocrinology, Metabolism and hypertension, Tel Aviv-Sourasky Medical Center*
[3]*Interventional Radiology, Department of Imaging, Tel Aviv-Sourasky Medical Center*
[4]*Department of Internal Medicine, Tel Aviv-Sourasky Medical Center*
[5]*The Sagol Center for Epigenetics, The Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel, Tel Aviv, Israel.*

AVS is crucial for diagnosing primary aldosteronism (PA), relying on cortisol-based selectivity and lateralization indices (SI/LI). However, variability in cortisol levels and aldosterone-cortisol co-secretion can hinder diagnostic accuracy. A multicomponent lateralization index incorporating 17-hydroxyprogesterone (17OHP) and the contralateral suppression index (CSI) may improve subtype differentiation between aldosterone-producing adenoma (APA) and bilateral hyperaldosteronism (BHA). In this study, AVS without cosyntropin stimulation was conducted on 27 patients, with 25 successful procedures (14 APA, 11 BHA). Clinical and laboratory data highlighted key differences: APA patients exhibited lower plasma renin activity (0.06 ± 0.04 vs. 0.17 ± 0.13ng/ml/min) and higher aldosterone concentration (38 ± 20 vs. 25 ± 10.3 ng/dL) than BHA patients. APA patients also showed elevated aldosterone-to-cortisol (19.7 ± 14.2 vs. 1.9 ± 0.5), aldosterone-to-17OHP (35.3 ± 44 vs. 4.5 ± 5.2), and aldosterone-to-DHEAS ratios (26.7 ± 33.9 vs. 2.63 ± 1.7). Metabolic abnormalities, including diabetes (3 cases) and impaired fasting glucose (7 cases), and abnormal 1mg dexamethasone suppression test (1 case) were more prevalent in APA than in BHA (1 and 2 cases, respectively). Surgical intervention was performed in 12 APA patients, compared to 1 in the BHA group. We suggest a multicomponent index that improves the interpretation of AVS when LI values are borderline. Index includes cortisol-corrected LI (cutoff4), 17OHP LI (cutoff5), and CSI (≤0.5 for cortisol or 17OHP-corrected CSI3). For example, in a suspected APA case with borderline cortisol LI (2.96), the addition of aldosterone/17OHP LI (5) and CSI (0.5) solidified the diagnosis which was then confirmed by surgical cure. Conversely, reliance on marginally positive lateralization such as cortisol LI (4.01) and 17OHP LI (5.14) was offset by high CSI 4 which correctly predicted poor postoperative outcomes. Notably, indices derived from DHEA-S were not helpful in refining diagnoses. These findings highlight the advantage of integrating 17OHP-derived LI and CSI into AVS analyses to enhance diagnostic precision for PA subtyping. Further studies are needed to establish refined cutoff values and to facilitate routine use of 17OHP in clinical practice.

177

Pancreatitis duration and severity depend on pericytic TLR/MyD88-mediated response

Mohammed Egbaria[1], Anat Schonblum[1], Lena kabha[1], Dunia Ali naser[1], Shani Puyskey[1], Daniel Korenfine[1], Limor Landsman[1]
Gray faculty of medicine, Tel-Aviv University

Pancreatitis, one of the leading causes of pancreatic adenocarcinoma (PDAC), arises from damage to the exocrine pancreas. While in most cases, pancreatitis resolves after tissue damage is repaired and the pancreas regenerates, failure in regeneration can lead to chronic pancreatitis, significantly increasing the risk of PDAC development. Pericytes, the mural cells surrounding endothelial cells in small blood vessels, contribute to tissue remodeling and fibrosis in various tissues. Our published studies showed that pancreatic pericytes express cytokines downstream of the TLR/MyD88 pathway, which mediates the cellular response to tissue damage. Our preliminary findings further reveal that pericytes become activated in response to caerulein-induced tissue damage, adopting a myofibroblast-like phenotype. We hypothesized that the TLR/MyD88-dependent pericytic response to pancreatitis-associated tissue damage is crucial for exocrine regeneration. To test this hypothesis, transgenic mice harboring a selective deletion of the Myd88 gene in pancreatic pericytes were treated with caerulein to induce acute pancreatitis. As expected, the loss of MyD88 affected the pericytic response to tissue damage. Notably, this impaired pericytic response led to compromised regeneration of the exocrine tissue, with sustained loss of acinar identity. Furthermore, we observed more severe tissue damage in mice lacking pericytic MyD88 expression. Thus, we showed that pericytes, and their transition to myofibroblasts are essential for proper regeneration of the exocrine pancreas following damage

**I would like to present poster also if its possible.

178

Association between Somatic Mutations in Cortisol-Secreting Adrenal Adenomas and Clinical-Demographic Features: A Single-Center Study of 112 Cases

Hadas Rabani[1], Nina Nazarov[2], Hila Shefer[2], Mohammad Sheikh-Ahmad[1,3], Anan Shalata[1], Katya Jovanovic[1], Jacob Bejar[2], Leonard Saiegh[1,3]

[1]*Endocrinology department, Bnai Zion Medical Center*

[2]*Pathology department, Bnai Zion Medical Center*

[3]*The Ruth and Bruce Rappaport Faculty of Medicine, Technion*

Cortisol-producing adrenal adenomas (CPAs) account for 20–50% of adrenal masses. The clinical presentation varies between mild autonomous cortisol secretion (MACS) and overt Cushing`s syndrome (OCS). Mutational analysis of CPA allows improved understanding of the pathogenic mechanisms underlying autonomous cortisol production. Somatic genetic alterations have been identified in 50–70% of CPAs, with PRKACA, GNAS, and CTNNB1 mutations being the most commonly detected.

In this study, we performed targeted mutational analysis of 112 CPAs from patients who underwent adrenalectomy at our medical center between 2008 and 2023. 31 patients (27.6%) were diagnosed with OCS, and 81 patients (82.3%) with MACS. Formalin-fixed adrenal gland specimens were immunohistochemically stained for CYP11B1 (11β-hydroxylase), and in each specimen, the most intensely stained adenoma was sampled and processed for DNA extraction. The DNA samples were then analyzed using RT-PCR to detect five known mutations: PRKACA p. L206R, CTNNB1 p.S45P and p.S45F, and GNAS p.R201H and p.R201C.

Mutational analysis revealed that 54% of CPAs harbored at least one mutation. The most frequent mutation in our cohort was CTNNB1 p.Ser45Pro, detected in 21% of samples. Most CPAs carried a single somatic mutation, with only five cases (8.3% of mutation-positive CPAs) exhibiting double mutations, four of these combined CTNNB1 p.Ser45Pro with GNAS p.Arg201Cys. The PRKACA p. L206R mutation was detected more frequently in OCS compared with MACS patients (16% vs 4.9% respectively), while CTNNB1 p.Ser45Pro mutation was more prevalent in MACS patient (13% vs 25%, respectively). None of the patients with OCS harbored one of the two GNAS mutations examined, in contrast to 14 (17.2%) of patients with MACS.

In conclusion, our study demonstrated that using a targeted panel of only five mutations, detects alterations in over 50% of CPAs. In addition, different types of mutations were associated with distinct clinical manifestations.

GLP-1-Receptor Agonists Directly Reduce Proliferation in ATDC5 Chondrocytes

Irit Meivar Levy[1,2], Biana Shtaif[1,3], Galia Gat-Yablonski[1,3], Moshe Phillip[1,3], Naama Fisch-Shvalb[1,3]

[1]*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center*

[2]*Felsenstein Medical Research Center*

[3]*Gray Faculty of Medical and Health Sciences, Tel, Tel Aviv University*

Aims: Long-acting glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as highly effective pharmacologic agents for obesity management. GLP-1RAs are currently approved for the treatment of obesity in children older than 12 years and for type 2 diabetes mellitus in children older than 10 years. However, their effects on linear growth in children remain poorly characterized. Our aim was to assess whether there is a direct effect of GLP1-RAs on the epiphyseal growth plate in ATDC5 cells, a well-established in-vitro chondrogenic model.

Methods: We analyzed the expression of GLP-1R in ATDC5 cells using reverse transcription -PCR and immunofluorescence analyses. Exendin-4, a GLP-1RA, was used to evaluate the receptor`s activity and the impact of GLP-1R activation on cell proliferation.

Results: GLP-1R mRNA was detected in naïve ATDC5 cells and throughout chondrocyte differentiation. Exposure to Exendin-4 for 5 to 30 minutes resulted in a significant elevation of intracellular cAMP levels. In insulin, transferrin, and Selenium (ITS)-induced ATDC5 cells, treatment with Exendin-4 led to a marked decrease in cell proliferation, as demonstrated by direct cell counting, the colorimetric CCK-8 assay, a significant downregulation of Ki67 mRNA expression, and a reduction in the percentage of Ki67-positive cells.

Conclusions: We demonstrate for the first time that GLP1-Rs are present and active in ATDC5 chondrocytes, and their activation by Exendin-4 reduces chondrocyte proliferation rate, suggesting a direct effect of GLP1-RAs on the murine growth plate. These results warrant further investigation of potential effects of GLP1-RAs on linear growth.

181

Clinical Significance of Infiltrative vs Encapsulated Follicular-Variant Papillary Thyroid Carcinoma: A Questionnaire Study

Amit Arbel[1], Dania Hirsch[1,2], Amit Ritter[1,3]
[1]*Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[2]*Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel*
[3]*Department of Otolaryngology, Head and Neck Surgery, Rabin Medical Center, Petach Tikva, Israel*

Background

In recent years, follicular variant papillary thyroid carcinoma (FVPTC) has been subclassified as infiltrative (non-encapsulated) or encapsulated. These subtypes behave similarly to classic PTC with BRAF-like mutations, or to follicular thyroid carcinoma (FTC) with RAS-like mutations, respectively. This study evaluated how a team of expert physicians manage infiltrative and encapsulated FVPTC compared with classic PTC or FTC.

Methods

A cohort of 100 FVPTC cases from a tertiary center was generated. For each patient, a treatment questionnaire was created along with a control questionnaire with an identical clinical profile but a different histological label: for infiltrative FVPTC—a classic PTC control; for encapsulated FVPTC—an FTC control. Eight expert physicians (4 endocrinologists, 4 head and neck surgeons) were interviewed. In total, 800 questionnaires were completed (400 pairs).

Results

Among the FVPTC cases, 34.7% were encapsulated and 65.3% infiltrative. The mean age was 45.9 years, 76% were female, and the average tumor size was 19 mm. Extrathyroidal extension was present in 26%, vascular invasion in 3%, and lymph node involvement in 22%. Lobectomy was performed in 60% of cases, and total thyroidectomy (with or without neck dissection) in 40%. In 229 paired questionnaires initially treated with lobectomy, completion thyroidectomy was recommended in 13.1% of cases and 14.9% of controls (NS). In 96.5% of pairs, both cases received the same recommendation. Discordant decisions were rare (3.5%), and were more common when the control was classic PTC. In 190 case-control pairs eligible for RAI, recommendation rate was similar between groups, with 93.7% concordance. Discordant choices were more common in FTC questionnaires and head-and-neck surgeons (66.7%) .

In the 84 pairs where RAI therapy was recommended, physicians chose identical RAI doses in 85% of cases. Overall, there was no statistically significant difference in dosing between groups ($p = 0.167$).

Conclusions

Although FVPTC is a distinct histological entity with infiltrative and encapsulated subtypes, in most cases, treatment decisions resembled those for classic PTC or FTC. The additional subtyping added complexity without improving clinical decision-making, raising the question of whether the two FVPTC subtypes should be incorporated into classic PTC and FTC for guiding treatment decisions.

182

Efficacy and Safety of RFA Therapy in Patients with Benign Thyroid Nodules Compared to Other Modalities

Roni Mechorish[1], Moshe Yehuda[1,2], Eyal Robenshtok[1,3], Hadar Duskin-Bitan[1,3], Gideon Bachar[1,2], Ilan Shimon[1,3], Ido Amir[1,2]

[1]*Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

[2]*Department of Otolaryngology, Head and Neck Surgery, Rabin Medical Center, Petach Tikva, Israel*

[3]*Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel*

Background: Lobectomy had been a standard treatment for large and/or functioning thyroid nodules for many years, but may lead to postoperative hypothyroidism and visible scarring. Radiofrequency ablation (RFA) offers a minimally invasive alternative with preserving normal of thyroid tissue. Comparative outcome data from Israel remain limited.

Methods: A retrospective cohort study was conducted at Rabin Medical Center (2020–2025) including 206 adults with benign thyroid nodules: 116 treated with RFA and 90 with lobectomy. Demographic variables, thyroid function (TSH, FT4, FT3), need for chronic LT4 or antithyroid therapy, nodule volume change, and adverse events were assessed. The primary outcome was maintenance of euthyroidism; secondary outcomes included volume reduction and safety.

Results: Patients treated with RFA were younger (mean 48.8 vs. 57.9 years) and predominantly female (106/116 vs. 67/90). RFA preserved thyroid function in almost all cases, with 0/116 requiring chronic levothyroxine, compared to 15/90 (17%) after lobectomy. RFA achieved a mean nodule volume reduction of 66±7%, while no comparable data was available after lobectomy due to complete lobe excision. Early voice-related symptoms occurred in 14/90 (15.6%) after lobectomy vs. 8/116 (6.9%) after RFA, and permanent vocal cord paralysis in two lobectomy patients (2.2%) and one RFA patient (0.9%).Postoperative swallowing discomfort was reported in 5/90 (5.6%) vs. 4/116 (3.4%), respectively. RFA did not create a scar.

Conclusion: In this cohort, RFA provided a practical and safe alternative to lobectomy, maintaining euthyroidism, achieving substantial volume reduction, and resulting in fewer long-term hormone requirements and fewer local complications, without surgical scarring. These findings support the integration of RFA into routine practice for selected patients with benign thyroid nodules.

183

An oral glucose tolerance test in pregnancy and its association with future cardiovascular diseases

Tal Schiller[1,2], Linoy Gabay[3], Oren Barak[4], Alena Kirzhner[5], Edi Vaisbuch[4], Haitham Abu Khadija[6], Gabriel Chodick[7], Yael Barer[2]

[1]*Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, Institute of Endocrinology, Diabetes and Metabolic Disease, Wolfson Medical CEnter*

[2]*Kahn-Sagol-Maccabi Research and Innovation Institute, Maccabi Healthcare Services, Tel Aviv, Israel*

[3]*Wolfson Medical Center, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

[4]*Department of Obstetrics and Gynecology, Kaplan Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*

[5]*Department of Internal Medicine A, Kaplan Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*

[6]*Department of Cardiology, Kaplan Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*

[7]*School of Public Health, Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel*

Aims/hypothesis: Gestational diabetes and abnormal 100-gram oral glucose tolerance test (OGTT) results in pregnancy are associated with type 2 diabetes, but their relationship with cardiovascular disease (CVD) is less clear. We evaluated the risk of CVD according to the number of abnormal OGTT values during pregnancy.

Methods: This retrospective cohort study used data from a major Israeli healthcare provider. Pregnant individuals aged 20 to 50 years without a prior diagnosis of type 2 diabetes and CVD who had a complete 100-gram OGTT during their last pregnancy between January 2000 and December 2022 were included. The primary outcome was the development of a composite of CVD by September 2024. Risk was assessed using Cox proportional hazards models based on the number of abnormal OGTT values.

Results: The study included 103,389 individuals with a mean age of 34 ± 5.2 years. Overall, the median follow-up was 6.8 years (IQR, 3.4–12.9), totaling 886,955 person-years. A composite of CVD developed in 641 individuals (a cumulative incidence of 0.62%). When compared to individuals with all OGTT values normal, individuals with one to three abnormal values had an adjusted hazard ratio (HR) of 1.2 (95% CI: 1.02–1.4) for CVD, reaching 2.41 (95% CI 1.44-4.05) in those with four abnormal OGTT values.

Conclusions: A history of abnormal 100-gram OGTT results in pregnancy, and specifically having four abnormal values, is associated with an elevated risk of CVD. These results underscore the need for early post-partum identification and prevention strategies in this high-risk population.

184

Prognostic Factors and Survival in Patients with Bone Metastases from Thyroid Cancer

Noga Odess[1], Liyona Kampel[1,2], Anton Warshavsky[1,2], Gilad Horowitz[1,2], Eyal Robenshtok[1,3], Nidal Muhanna[1,2], Inbar Finkel[1,4]

[1]*Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

[2]*Department of Otolaryngology, Head and Neck and Maxillofacial Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

[3]*Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel*

[4]*Head and Neck Medical Oncology Unit, Division of Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

Background: Bone metastases from thyroid cancer represent an uncommon but clinically significant manifestation associated with substantial morbidity. We aimed to evaluate the prognostic implications of bone metastases and identify factors underlying an aggressive clinical course.

Methods: A retrospective review of patients with thyroid cancer and bone metastases treated at Tel Aviv Sourasky and Rabin Medical Centers between 1985 and 2024. Clinical, histopathologic and molecular data were collected. Survival outcomes were analyzed from the time of bone metastases diagnosis.

Results: Fifty-nine patients were identified: 38 (64%) with papillary, 11 (19%) with follicular, 6 (10%) with poorly differentiated, and 4 (7%) with Hürthle cell carcinoma. The median age at bone metastases diagnosis was 63 years (range, 21–89), with a median interval of 80 months from primary tumor diagnosis. At bone metastases presentation, 31 patients (52%) had additional distant metastases, predominantly pulmonary (75%). Thirty-two tumor samples underwent next-generation sequencing, most frequently revealing BRAF or NRAS alterations. The median overall survival after bone metastases diagnosis was 47 months. Patients who developed bone metastases while receiving systemic therapy demonstrated significantly shorter survival than those who were treatment-naïve (30.4 vs. 79 months, P = 0.002). Axial skeletal involvement was most frequent (31 patients, 52%), followed by perpendicular (11, 18%) and combined axial–appendicular disease (17, 29%). Treatment modalities included radioactive iodine, external beam radiation, and systemic biologic therapies.

Conclusion: Bone metastases in thyroid cancer are associated with poor prognosis, particularly when they emerge during systemic treatment, suggesting a biologically aggressive and treatment-refractory disease phenotype.

185

Epigenetic adaptation of beta cells across lifespan and disease: age-related demethylation is advanced in type 2 diabetes

Dana Avrahami Tzfati[1], Elisabetta Manduchi[2,3], Hélène C. Descamps[2,3], Klaus H. Kaestner[2,3], Jinping Liu[2,3], Jonathan Schug[2,3], Benjamin Glaser[4], Ali Naji[5]

[1]*Department of Developmental Biology and Cancer Research, Hadassah Medical school, Hebrew University, Jerusalem, Israel*

[2]*Institute of Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

[3]*Department of Genetics, University of Pennsylvania, Philadelphia, PA*

[4]*Department of Endocrinology and Metabolism, Hadassah Medical Center, Faculty of Medicine, Hadassah Medical Center, Hebrew University of Jerusalem, Israel*

[5]*Department of Surgery and Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Although the prevalence of type 2 diabetes (T2D) increases with age, most adults maintain normoglycemia despite rising insulin resistance, largely due to the adaptive capacity of pancreatic beta cells to meet increased metabolic demand. However, persistent insulin resistance can lead to beta cell dysfunction and T2D onset. Here, leveraging cell-type-specific methylome data from the Human Pancreas Analysis Program (HPAP), we investigate the epigenomic basis of beta cell adaptation by mapping genome-wide DNA methylation (DNAm) patterns across the human lifespan. In healthy donors, we identify progressive age-related demethylation enriched in cis-regulatory elements at beta cell identity and function genes, suggesting that epigenetic remodeling supports functional adaptation to metabolic demand over time. In contrast, alpha cells show the opposite trajectory, with subtle, age-related hypermethylation. In T2D beta but not alpha cells we observed further demethylation compared to healthy controls, underscoring a unique capacity of beta cells to respond to changes in metabolic demand. Together, our findings suggest that DNAm remodeling in healthy beta cells reflects a long-term adaptation to metabolic demand, which in T2D is accelerated as part of a compensatory response that ultimately fails under sustained insulin resistance.

186

Paternal ketogenic diet programs offspring liver metabolism and physical activity

Miri Stolovich-Rain[1], Jamie Magrill[1], Saja Baraghithy[2], Rachel Ben-Haroush Schyr[1], Elad Ben-Cnaan[2], Evgenia Volinsky[3], Danny Ben-Zvi[1], Benjamin Glaser[4], Joseph Tam[2], Yuval Dor[1]

[1]*Faculty of Medicine, Department of Developmental Biology and Cancer Research, Hebrew University of Jerusalem, Institute for Medical Research Israel-Canada*

[2]*School of Pharmacy, Obesity and Metabolism Laboratory, Hebrew University of Jerusalem, Institute for Drug Research*

[3]*Endocrinoligy and Fertility lab, Shaare Zedek Medical Center*

[4]*Endocrinology and Metabolism Service, Hadassah University Hospital*

Paternal preconception diets reprogram offspring metabolism, but the effects of ketogenic diet, despite widespread human popularity for metabolic health benefits, have not been explored. Male mice fed ketogenic diet ad libitum for one month, the duration of sperm formation, developed sustained ketosis with elevated testicular ketones. Progeny of keto fathers (keto-pups) showed normal body weight, glucose homeostasis, and insulin sensitivity but markedly increased energy expenditure, fat oxidation, and voluntary activity vs. controls. Keto-pup livers exhibited lipid accumulation, glycogen depletion, expanded glutamine synthetase expression domains, CD45+ inflammatory foci, and increased hepatocyte turnover relative to controls. Consistent with fatty liver-induced inflammation and proliferation, liver transcriptomes of keto-pups revealed interferon responses, proliferation signatures, and a reduction in gene pathways associated with liver function. Paternal ketogenic diet programming of offspring metabolism may reflect evolutionary adaptation to starvation via ketosis, but in modern life it has potentially deleterious effects on next-generation health.

187

Stimulated Aldosterone Levels in Obesity

Yael Sofer[1,2], Esther Osher[1,2], Gabi Shefer[1,2], Yona Greenman[1,2], Naftali Stern[1,2]
[1]*Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center*
[2]*Gray faculty of Medical and Health Sciences, Tel Aviv University*

Background: Prior studies report elevated basal aldosterone in people with obesity, while ACTH-stimulated levels appear similar to lean controls.

Objective: To compare basal and ACTH-stimulated aldosterone responses to a 1-µg intravenous ACTH bolus in healthy adults with obesity versus lean controls.

Methods: Serum aldosterone and cortisol were measured at baseline and following 1-µg ACTH in 24 adults with obesity (mean BMI 36 kg/m²) and 18 lean controls (mean BMI 23 kg/m²). Age and sex distribution were comparable. All participants were normotensive, though blood pressure was higher in the obesity group (122±13.5/76.3±9.2 vs 113.6±7.1 mmHg).

Results: Baseline log10 -transformed aldosterone was positively correlated with waist/height ratio (r=0.38, p=0.058) but not BMI. log10 transformed aldosterone at 20 minutes was 30% higher in subjects with obesity as compared to controls (p=0.038). Area over the curve (AUC) of log10 transformed aldosterone was also nonsignificantly higher in the group with obesity (p=0.065). AUC of aldosterone to cortisol ratio was significantly higher in subjects with obesity as compared to controls (p=0.046).

Conclusion: Individuals with obesity demonstrate an enhanced aldosterone response to low-dose ACTH stimulation. The significantly higher aldosterone-to-cortisol ratio suggests a specific shift toward increased mineralocorticoid output in obesity, potentially serving as an early driver for blood pressure elevation and increased cardiovascular risk.

188

The role of sex in achieving weight loss after one anastomosis gastric bypass surgery

Ido Sarig[1,2], Wiessam Abu Ahmad[3], Yona Greenman[1,2], Yael Sofer[1,2]
[1]*Institute of Endocrinology, Sourasky Medical Center*
[2]*Gray faculty of medical and health sciences, Tel Aviv University*
[3]*Faculty of Medicine, The Hebrew University of Jerusalem*

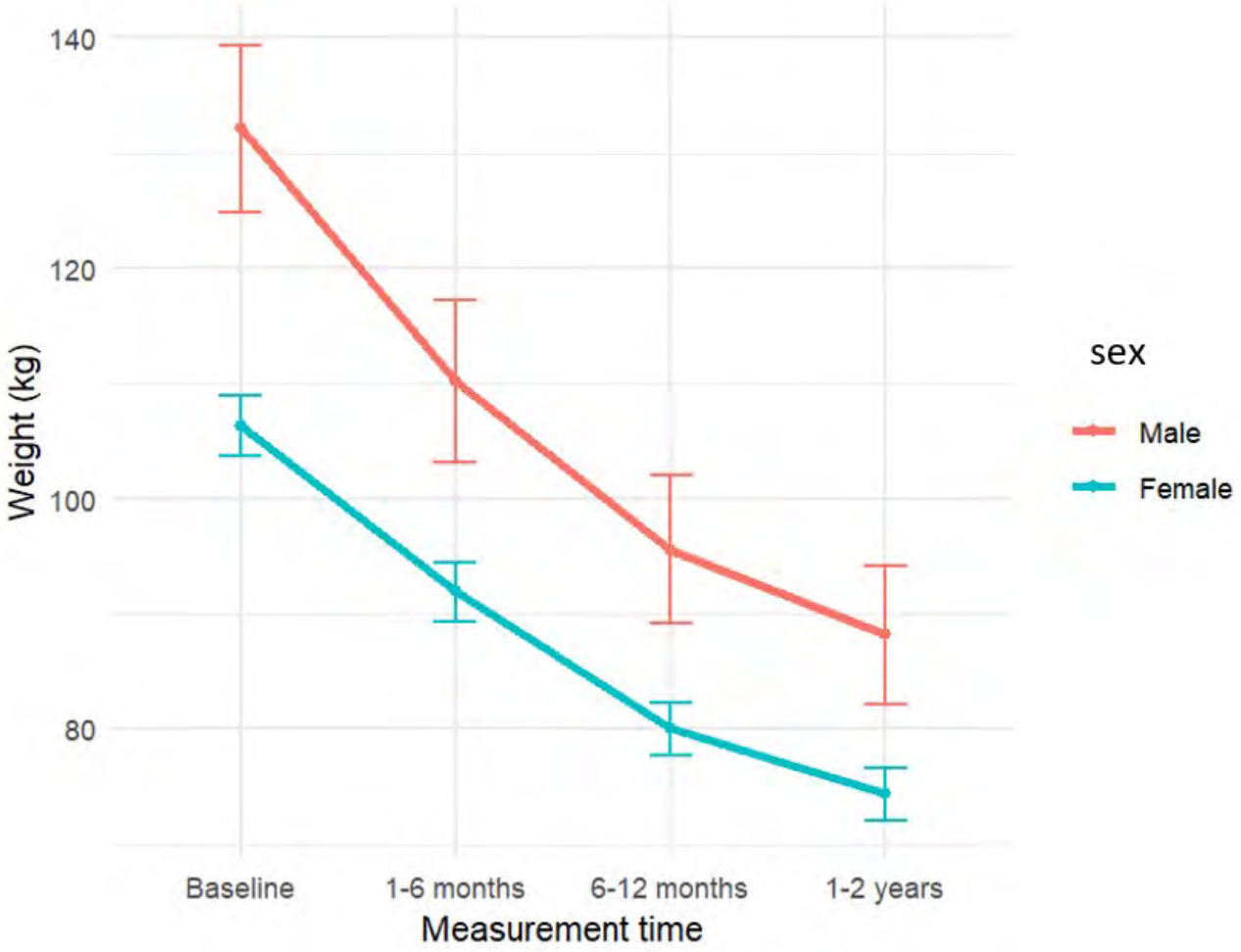
Background :Bariatric surgery (BS), is a highly effective and cost-efficient intervention for achieving long-term weight loss in individuals with obesity. In recent years, the One Anastomosis Gastric Bypass (OAGB) procedure has gained popularity in Israel, accounting for approximately 70% of all bariatric surgeries performed. Assessing the success of BS often involves measuring the total and mean percentage of excess weight loss (%EWL). While various factors predict %EWL, the impact of sex on this outcome remains controversial, with conflicting results in both general BS and specifically in OAGB studies.

Aims : Evaluate sex-specific differences in postoperative outcomes during the first two years after OAGB.

Methods: We conducted a retrospective cohort study among patients who underwent OAGB procedure at a single tertiary hospital. Data was obtained from medical records of the patients who underwent both preoperative and postoperative evaluations in the obesity clinic between 2013 and 2023. The primary outcome was the total and %EWL at 6-month, 1-year, and 2-year intervals following the procedure. Using a multivariant analysis we calculated weight loss and %EWL according to sex.

Results: A total of 187 patients were included, 133 (71.1%) females, 54 (28.9%) males. Median age was 46.7 (34.8-55.5) years for women and 49 (39.5-58.8) years for men (NS). Over time, participants experienced significant weight reductions. At 6-12 months post-surgery, the total weight decreased by 20.4 (15.1-26.2) kg relative to the baseline, and by 1-2 years, median weight loss was 36.2 (29-48.1) kg. Sex differences were observed, where males experienced higher weight reductions over time. At 6-12 months, males lost 20.4 (15.1-26.2) kg whereas women lost 15.4 (10.4-21.4) kg. Likewise, at 1-2 years, males experienced a weight reduction that was 12 kg more than that of females [(44.4 (36.8-51.7) kg compared to 32.4 (24.7-40.6) kg; p0.01]. This difference remained significant even after multivariate analysis, which accounted for factors such as age, underlying chronic conditions (including diabetes, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea), glucose and HbA1c levels and medications (insulin, statins, calcium channel blockers). %EWL was also significantly lower for men, 85+/-29% compared to 77+/-28% (p0.05).

Conclusion: This study highlights the significant impact of sex on weight loss outcomes following OAGB. Further research is warranted to explore the underlying mechanisms and potential implications for treatment strategies and patient counseling to optimize outcomes for both male and female patients.


140
120
100
80
Weight (kg)
Baseline
1-6 months
6-12 months
1-2 years
Measurement time
sex
Male
Female

189

Mitigation of Strength-Loss in Aged Mice: Therapeutic Efficacy of three compounds

Gabi Shefer[1], Gilad Lehmann[1], Miguel Morales Moshiashvili[1], Yonit Marcus[1], Yona Greenman[1]

Endocrinology, Tel-Aviv Sourasky Medical Center

Background: Age-related decline in muscle function (dynapenia) often progresses faster than loss of muscle mass, making preservation of force-generating capacity a research priority. We screened 11 nutraceuticals previously reported to support muscle growth and identified a three-compound combination—quercetin, hesperetin, and ursolic acid (Trio)—that outperformed individual components in C2C12 myotube assays, indicating synergistic action.

Objective: To evaluate the effects of Trio supplementation on grip strength and body composition in aged mice.

Methods: Thirty-six female mice (17 months old) were allocated to Treatment (n=17) or Control (n=19) groups, matched for body weight and baseline grip strength. Trio was administered via drinking water for 6 weeks; vehicle consisted of 0.5% DMSO and 0.5% soy lecithin. Control mice received vehicle alone. Grip strength was assessed pre- and post-intervention. To ensure statistical rigor, body weight comparisons were analyzed using a t-test (assuming unequal variance). The ratio of muscle mass to total body weight was analyzed following an arcsine square-root transformation to achieve normal distribution, followed by a t-test (assuming unequal variance). Longitudinal changes in grip strength were evaluated using a repeated-measures ANOVA.

Results: No baseline differences in grip strength or body weight were observed between groups. Both groups exhibited significant grip strength decline over the study period (p0.05). However, the Treatment group demonstrated markedly attenuated loss compared to Control (Treatment: 53.2→47.4, −11%; Control: 51.8→39.7, −23%; repeated-measures ANOVA interaction p=0.03). Despite divergent functional outcomes, no significant differences in body weight or muscle-to-body mass ratio were detected post-treatment (p0.05), though a trend toward preserved muscle mass was observed in the Treatment group.

Conclusions: Trio supplementation significantly mitigated age-related grip strength decline in mice. Notably, functional preservation occurred without significant changes in muscle mass, indicating an effect on muscle quality rather than quantity. This represents a novel demonstration that a defined nutraceutical combination can selectively protect age-related muscle function without significantly increasing muscle mass. These results highlight the Trio-treatment as a promising, low-burden intervention that may target neuromuscular efficiency, or contractile protein integrity. Given that dynapenia, not sarcopenia, per-se drives loss of independence and disability in older adults, the functional preservation observed here after only 6-weeks of treatment, underscores the potential translational importance of this approach.

190

Dynamic lifestyle-induced changes in asymmetric dimethylarginine (adma) correlate with alteration in lipid profile and fasting insulin in subjects with the metabolic syndrome

Brurya Tal[1], Gabi Shefer[1], Jessica Sack[1], Yonit Marcus[1], Yael Sofer[1], Marianna Yaron[1], Limor Ben Haim[1], Elena Izhakov[1], Yona Greenman[1], Naftali Stern[1]

The Sagol Center for the Metabolic Syndrome, Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center; Sackler Faculty of Medicine, Tel Aviv University, Israel

Background: Elevated levels of Asymmetric Dimethylarginine (ADMA) are linked to a higher incidence of Major Adverse Cardiovascular Events (MACE). ADMA is a significant predictor of MACE, independent of other risk factors such as age, sex, blood pressure, smoking history, and diabetes. It is known to inhibit nitric oxide synthase, reducing nitric oxide production and potentially causing endothelial dysfunction. ADMA could be a valuable diagnostic tool for cardiovascular risk assessment, though its integration into current risk scores requires further validation.

Methods: A cohort of 75 participants (33 men and 42 women) diagnosed with Metabolic Syndrome (MS) according to ATPIII criteria, underwent a 1-year intensive multidisciplinary treatment. This included personalized physical training and a low-calorie, high-protein Mediterranean diet. Baseline characteristics were mean±SD: age 53.3±11.2 years, weight 99±17 kg, BMI 34.5±4 kg/m², ADMA 0.5±0.2 µmol/L, L-Arginine 45±15 µmol/L, triglycerides (TG) 193±85 mg/dL, cholesterol 190±35 mg/dL, and insulin 26±18 µIU/mL.

Results: After one year, participants experienced a 9% reduction in BMI (p0.0001), a 10% reduction in cholesterol only in men (p0.0001), and a 27% reduction in TG (p0.05 in women, and p0.0001 in men). ADMA levels decreased by 17% (p=0.036 for women, p=0.0064 for men). L-Arginine levels increased by 14% but did not reach statistical significance. Significant correlations were observed between changes in ADMA and: insulin (r=0.51; p0.05), cholesterol (r=0.38; p0.05), TG (r=0.36; p0.05).

Conclusion: In the metabolic syndrome, lifestyle modifications, including a Mediterranean diet rich in protein and weight loss achieves reduction in ADMA levels which is linked to changes in classical risk factors such as serum cholesterol, triglycerides and insulin.

191

BRAF and MEK inhibitors other than Dabrafenib and Trametinib for advanced thyroid cancer

Tzahi Yamin[1], Oded Cohen[1], Eyal Robenshtok[2,3], Inbar Finkel[3,4]
[1]*Department of Otolaryngology, Head and Neck Surgery, Assuta Samson Ashdod Medical Center, Ashdod, Israel*
[2]*Endocrinology & Metabolism Institute, Rabin Medical Center, Petach Tikva, Israel*
[3]*Gray School of Medicine, Tel-Aviv University, Tel-Aviv*
[4]*Department of Oncology, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel*

Background and Objective: BRAF V600E mutation is the most common and clinically significant genetic alterations in advanced thyroid cancers. This study provides real world experience with BRAF and MEK inhibitors other than dabrafenib and trametinib in the treatment of advanced thyroid cancers harboring BRAF V600E mutation.

Methods: A case series of four patients with advanced thyroid cancer (three papillary and one anaplastic thyroid cancer) treated with various BRAF and MEK inhibitors. All patients had confirmed BRAF V600E mutation.

Results: Among three patients treated with BRAF/MEK inhibitors for radioiodine refractory metastatic PTC, and one patient with ATC, all (100%) demonstrated partial response (PR) during therapy, yielding an overall response rate (ORR) of 100%. Stable disease was also observed in multiple treatment phases, contributing to a high overall disease control rate. Three patients had disease-related death, while one remained under treatment at last follow-up. Course of treatment was complicated by significant toxicities, including encephalopathy, pancreatitis, capillary leak syndrome and major allergic reaction, leading to treatment discontinuations. Despite initial responses, all cases eventually progressed, necessitating sequential treatment strategies. The observed overall survival ranged from 6.0 to 25.3 months, with a median follow-up of 18.3 months since the initiation of BRAF and MEK inhibitor therapy.

Conclusion: This case series highlights the potential benefits and challenges of targeted therapies in advanced thyroid cancer. While BRAF and MEK inhibitors offer new treatment options, toxicity management and the development of resistance remain significant hurdles. The limited FDA-approved options for BRAFV600E positive thyroid cancer compared to melanoma underscore the need for further research to optimize treatment strategies, toxicities management and expand therapeutic options for these challenging malignancies.

192

Identifying transcription factor programs responsible for pituitary stem cell differentiation into gonadotropes in the neonate using single-cell multiomics

Gil Golan[1], Daniel Sheridan[2], Karine Rizzoti[2], Robin Lovell-Badge[2], Philippa Melamed[1]
[1]*Faculty of Biology, Technion-Israel Institute of Technology*
[2]*Francis Crick Institute*

In addition to the various endocrine cell populations, the anterior pituitary contains pituitary stem cells (PSCs) which can differentiate into all hormone-producing cells. However, in the neonate they differentiate primarily into gonadotropes, and most adult gonadotropes originate from this postnatal process. This neonatal wave of differentiation is thus central to the establishment of the functional reproductive axis in the adult, though the trigger and the underlying mechanisms remain unclear. We hypothesize that this process involves activation of distinct transcription factors (TFs), including pioneer factors that open chromatin. This chromatin remodeling ultimately drives expression of the gonadotrope-specific genes which establish the postnatal gonadotrope lineage. To investigate this, we generated and analyzed single-cell multi-omic data of PSC-derived cells from neonatal mice, capturing gene expression and chromatin accessibility in individual cells. These pituitary cells are in various stages of differentiation: from PSCs, through pre-gonadotropes that express several key TFs such as *Foxl2* and *Nr5a1*, to mature gonadotropes. Using SCENIC+ for systematic gene-regulatory network (GRN) analysis, we identified GRNs active at different stages. Each GRN includes the TF, its predicted target genes and candidate regulatory elements mediating its activity. We focused first on the Nr5a1 GRN, which includes known targets (*Cga*, *Gnrhr*) as well as novel candidate genes comprising TFs predicted to be active in differentiating gonadotropes. Our analysis indicates that Nr5a1 induces expression of these genes by binding their promoters and novel gene-specific enhancers. These regulatory interactions were confirmed using Nr5a1 CRISPR-mediated knockout in gonadotropes, and Nr5a1 overexpression in a PSC-like cell line. We also investigated *Foxl2* regulation during gonadotrope differentiation, and identified three putative enhancers potentially driving its expression. The accessibility of these enhancers increases throughout differentiation, in accordance with *Foxl2* expression. The pioneer TF Ascl1 is predicted to regulate *Foxl2*, and Ascl1 overexpression in the cell line elevated *Foxl2* RNA levels. ChIP-seq analysis confirmed Ascl1 binding to the *Foxl2* promoter and the distal enhancer elements in gonadotrope cells. Furthermore, CRISPR deletion of the *Foxl2* proximal enhancer reduced its expression at both RNA and protein levels. *Foxl2* downregulation was accompanied by changes in the chromatin landscape, as enhancer removal led to a reduction in activating histone modifications at the *Foxl2* promoter. Importantly, these enhancer sequences are conserved and open in human adult gonadotrope cells, suggesting roles also during human gonadotrope differentiation. Our findings thus reveal key TF-driven regulatory mechanisms guiding PSC differentiation into gonadotropes and advance our understanding of postnatal pituitary development.

194

Overweight, obesity, and all-cause illness-attributed workdays loss in a nationwide cohort of 481,067 young adults

Bar Weinstein[1,2], **Bar Lossos**[1,3], Jacob Megreli[1,3], Ma'ayan Shaked[1,3], Zivan Beer[1,3], Doron Yaya-Stupp[1,3], Meir Schechter[1,4]

[1]*Medical Data Research Institute, Israel Defense Forces Medical Corps, Tel HaShomer, Ramat Gan, Israel*

[2]*School of Mathematical Sciences, Tel Aviv University, Tel Aviv, Israel*

[3]*Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*

[4]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel*

Background:

Overweight and obesity in early adulthood were associated with increased risks of various long-term complications, including type 2 diabetes, chronic kidney disease, cardiovascular disease, and cancers. The association between overweight and obesity with all-cause illness-attributed workdays loss in young adults remains unknown.

Methods:

In a retrospective cohort study, we used a nationwide cohort of Israeli young adults recruited to military service (2017-2025). We excluded individuals who were medically unfit for service, who lacked a body mass index (BMI) measurement, or who were older than 25 years at recruitment. We linked electronic health data from the Israeli Defense Forces Medical Corps with military occupational data containing daily information on work attendance, absence, and sick leave specifically. These occupational data are adjudicated everyday by the individual's commander and human resources personnel. Individuals were stratified into underweight (sex- and age-matched BMI 5%), normal weight (5-85%; reference), overweight (85-95%), and obesity (≥95%) subgroups. For each participant, we calculated the proportion of all-cause illness-attributed workday loss per 100 workdays. The between-groups rate ratio was estimated using multivariable-adjusted Poisson lognormal models, adjusted for age, sex, recruitment year, residential socioeconomic status, birth country, prediabetes and diabetes, chronic kidney disease, mental health history, role assignment, and combat allocation.

Results:

The study included 481,067 young adults (44.0% women; mean age 18.4 years). There were 24,295, 24,052, 384,640, and 48,080 individuals with underweight, normal weight, overweight, and obesity, respectively. Among those with normal weight, there were 5.31 million reported illness-attributed workdays lost (2.6%) out of 204.59 million total workdays. The respective proportions in the underweight, overweight, and obesity subgroups were 2.4%, 2.9%, and 3.1%. The proportion of individuals with ≥2% of their workdays lost due to illness was 40.8%, 41.7%, 45.4%, and 48.1% among those with underweight, normal weight, overweight, and obesity, respectively. Compared with those with normal weight, the rate ratios for illness-attributed workdays lost were 0.91 [95% CI 0.90-0.93], 1.06 [1.04-1.07], and 1.08 [1.06-1.10] for underweight, overweight, and obesity, respectively. The respective rate ratios by sex were 0.86 [0.84-0.89], 1.07 [1.05-1.09], and 1.06 [1.03-1.08] in men, and 0.97 [0.94-0.99], 1.04 [1.02-1.06], and 1.10 [1.07-1.13] in women.

Conclusions:

In a nationwide cohort of young adults, overweight and obesity were associated with 6% and 8% increased rate ratio of all-cause illness-attributed workdays loss. These results highlight the morbidity and economic burden associated with overweight and obesity in young adults, even before long-term complications arise, supporting screening and intervention programs.

195

The Difficult Tribulations of the Endocrinologist in Diagnosing and Treating Tumor-Induced Osteomalacia: A Case Report and Literature Review

Auryan Szalat[1,2], Jeremy Godefroy[3], Karine A Atlan[4], Reut Book[5]
[1]*Endocrinology and Osteoporosis Clinic, Clalit Health Services, Jerusalem*
[2]*Department of Internal Medicine, Osteoporosis Center, Faculty of Medicine, Hebrew University of Jerusalem, Hadassah Medical Center*
[3]*Department of Medical Biophysics and Nuclear Medicine, Faculty of Medicine, Hebrew University of Jerusalem, Hadassah Medical Center*
[4]*Department of Pathology, Faculty of Medicine, Hebrew University of Jerusalem, Hadassah Medical Center*
[5]*Department of Otolaryngolology/Head and Neck Surgery, Faculty of Medicine, Hebrew University of Jerusalem, Hadassah Medical Center*

Introduction:
Tumor-Induced Osteomalacia (TIO) is a rare paraneoplastic syndrome caused by typically small, slow-growing phosphaturic mesenchymal tumors secreting excess fibroblast growth factor-23 (FGF23). This results in renal phosphate wasting, suppressed 1,25-dihydroxyvitamin D synthesis, and progressive osteomalacia. Due to nonspecific symptoms such as musculoskeletal pain, fatigue, and fractures, diagnosis is frequently delayed for years, leading to severe morbidity. The literature consistently highlights prolonged diagnostic odysseys, misdiagnoses, and the need for highly specialized biochemical and imaging approaches.

Clinical Case:
A 45-year-old previously healthy man presented with progressive severe back pain. Initial spinal CT revealed an L4–L5 disc herniation. Despite escalating analgesic therapy, including high-dose opioids, symptoms worsened. Subsequent MRI demonstrated multiple compression fractures throughout the lumbar spine and lower thoracic vertebrae. Bone scintigraphy showed widespread increased uptake involving the thoracic spine, sacroiliac joints, ribs, hips, knees, and feet. DXA revealed severe osteoporosis with a lumbar Z-score of −3.0.

Laboratory evaluation demonstrated hypophosphatemia (1.6 mg/dL), elevated alkaline phosphatase, normal parathyroid hormone levels, low 1,25-dihydroxyvitamin D, and renal phosphate wasting on 24-hour urine collection. After overcoming regulatory and logistical barriers, FGF23 levels were eventually measured and found to be elevated, strongly suggesting TIO. Empiric treatment with active vitamin D and calcium was poorly tolerated and ineffective. ^68Ga-DOTATATE PET/CT localized a hypermetabolic lesion in the left ethmoid sinus. An initial biopsy was technically successful; however, pathological analysis was inconclusive and interpreted as a benign vascular lesion, leading to postponement of surgical intervention. Only after direct multidisciplinary discussion between endocrinologists and pathologists did it become apparent that SSTR2 immunostaining had not been performed. At the request of the endocrine team, SSTR2 immunostaining was subsequently carried out, demonstrated strong positivity, and confirmed the diagnosis of a phosphaturic mesenchymal tumor. Two years after initial presentation, complete surgical resection resulted in rapid normalization of phosphate metabolism without supplementation which was further associated with significant improvement in well being and bone mineral density.

Conclusion:
This case illustrates the profound diagnostic and therapeutic challenges faced by endocrinologists managing TIO. Delays arise from nonspecific presentations, misleading pathology, limited access to specialized laboratory and imaging tests, and fragmented multidisciplinary communication. As supported by current literature, early recognition of hypophosphatemia, timely FGF23 measurement, functional imaging, and close collaboration between clinicians, nuclear medicine radiologists, surgeons, and pathologists are essential. Despite its rarity, heightened awareness of TIO is critical, as curative surgical resection can dramatically reverse morbidity and restore quality of life.

196

Nutraceutical Rescue of Methylprednisolone-Induced Myotube Atrophy: Evidence from C2C12 Morphometry

Gilad Lehmann[1], Yona Greenman[1], Yonit Marcus[1], Miguel Morales Moshiashvili[1], Gabi Shefer[1]

Endocrinology, Tel-Aviv Sourasky Medical Center (Ichilov)

Background: Glucocorticoid (GC) therapy frequently causes skeletal muscle wasting, yet safe adjunct strategies to preserve myogenesis are limited. Although individual nutraceuticals such as quercetin, hesperetin, and ursolic acid have each been reported to counter catabolic signaling, their combined impact on GC-suppressed myogenic fusion has not been systematically evaluated. Here, we asked to what extent the three-compound combination (Trio) could preserve myotube maturation under glucocorticoid stress, with testosterone serving as a positive control.

Methods: C2C12 myoblasts were differentiated into multinucleated myotubes and treated for 48 h with methylprednisolone alone (MP-only; 500 ng/mL), methylprednisolone plus testosterone (MP+T; 100 nM), or methylprednisolone plus Trio (quercetin 50 nM, hesperetin 2 μM, ursolic acid 1 μM). Myosin heavy chain–positive myotubes were quantified by automated ImageJ morphometry (myotube ROIs: MP n=277; MP+T n=275; Trio n=304). Myonuclear number per myotube was the primary endpoint; diameter and length were secondary. One-way ANOVA with Bonferroni correction tested group differences.

Results:
Glucocorticoid treatment alone yielded the lowest myonuclear number per myotube (96.0 ± 50.8). Both MP+T and the Trio group significantly increased myonuclear content (135.4 ± 56.5 and 143.1 ± 51.0, respectively), with a strong overall effect ($F(2,853)=65.0$, $p=5.2\times10^{-27}$). Each treatment differed from MP-only (p0.0001), whereas the two treatments did not differ from each other (p=0.25), indicating that the Trio achieved testosterone-level fusion rescue. Importantly, the Trio treatment significantly increased the number of multinucleated myotubes (16.2 ± 5.1 vs 13.4 ± 3.9; $F(2,853)=47.9$, $p=1.9\times10^{-20}$; p0.0001), whereas testosterone did not, highlighting a unique pro-fusion action. Effects on myotube size were modest: testosterone increased diameter and length (p=0.031 and p=0.040), whereas the Trio primarily enhanced fusion indices without robust hypertrophy. Cross-sectional area did not differ significantly across groups, consistent with fusion preceding overt growth.

Conclusions (Novelty and Significance):
This study provides the first evidence that a quercetin-hesperetin-ursolic acid combination restores myonuclear accretion under GC exposure to the same magnitude as testosterone, while surpassing testosterone in promoting multinucleated myotube formation. These findings identify a previously unrecognized strategy to dissociate early fusion rescue from androgen signaling and demonstrate that nutraceutical combinations can reach a functional “fusion ceiling” comparable to pharmacologic androgen support. The results support a model in which targeted multi-factor supplementation preserves myogenic differentiation at an early stage, offering a promising, potentially lower-risk adjunct for glucocorticoid-associated myopathy and other conditions characterized by impaired fusion.

197

Nuclear Receptors Activation Maintains Identity in Primary Mouse Hepatocytes During Culture

Yael Pelez Daniel[1], Ido Goldstein[1]
The Robert H. Smith Faculty of Agriculture, Food and Environment, Institute of Biochemistry, Food Science and Nutrition. The Hebrew University of Jerusalem.

The liver is one of the most important and complex organs in the body, as it plays a central role in metabolic homeostasis. Primary mouse hepatocytes (PMH) serve as a readily-available ex vivo model for studying metabolism, toxicology, and drug development. However, rapid hepatocyte dedifferentiation and loss of functions in culture remain major problems. PMH also undergo epithelial-to-mesenchymal transition (EMT), becoming more mobile and invasive, display elongated “fibroblast-like” morphology, and exhibiting reduced hepatic functions. Here, we aim to characterize hepatocyte deterioration in culture and explore ways to maintain hepatic identity in culture.

We performed RNA-seq analysis that revealed a significant transcriptomic gap between cultured PMH and freshly-isolated, non-plated hepatocytes. PMH plated for 48 hours show significant downregulation of CYP450 enzymes, hepatocyte-specific lineage-determining transcription factors and impaired response to hormonal cues, alongside upregulation of Mitogen-Activated Protein Kinase (MAPK) signaling and EMT markers. Notably, we found that the most pronounced transcriptional alterations do not occur within the first three hours after plating, indicating a critical intervention window. We found that early targeting of key nuclear receptors and transcription factors that are downregulated in culture, using specific agonists and their combinations within 3 hours after plating, enhances the maintenance of hepatic identity and gene expression. This early combinatorial nuclear receptor activation resulted in a marked upregulation of genes that are otherwise progressively downregulated in vitro. Moreover, inhibition of MAPK signaling further maintains hepatocyte identity by reducing EMT-associated markers while increasing the expression of CYP and nuclear receptor genes. Thus, early and combinatorial nuclear receptor targeting provides a more effective model for capturing key regulatory cues and studying hormone-dependent signaling and metabolic regulation.

These findings show that the cultured PMH model can be improved by small-molecules treatment and provide a foundation for further refinement of ex vivo models. An optimized hepatocyte culture system would enable more reliable investigation of drug metabolism and toxicity, and could serve as a physiologically relevant platform for studying hormone-regulated liver function and metabolic diseases.

198

Body mass index and incidence stress fractures in a nationwide cohort of 193,047 young women and men in combat training

Adi Horesh[1,2], Bar Weinstein[3], **Romi Halperson**[1,2], Omer Itzkovitch[1], Shlomi Abuhasira[1,2], Ziv Talmi[1,2], Ron Skorochord[1,2], Yitzchak Elefant[1,2], Yigal Chechik[1,4], Doron Yaya-Stupp[1,2], Aya Bardugo[1,2], Itay Ketko[1,2], Meir Schechter[1,5]

[1]*Medical Data Research Institute, Israel Defense Forces Medical Corps, Tel HaShomer, Ramat Gan, Israel*

[2]*Institute for Research in Military Medicine, Faculty of Medicine, Hebrew University of Jerusalem, Israel*

[3]*School of Mathematical Sciences, Tel Aviv University, Tel Aviv, Israel*

[4]*Department of Orthopedics, Shamir Medical Center, Be'er Yacob, Israel*

[5]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel*

Background:

Low body mass index (BMI) and reduced lean body mass have been associated with increased fracture risk in older adults. It is less clear whether low BMI is associated with reduced bone strength even at young adulthood. Combat training exposes the bone to repetitive stress forces, which may result in stress fractures, providing a good setting to assess this hypothesis. We assessed the association between BMI and incidence of stress fractures in young men and women enlisted for combat training.

Methods:

This nationwide, retrospective, cohort study included recruits to combat roles in the Israeli Defense Forces (IDF) between 2014-2024. Soldiers were grouped by their BMI measurement (18, 18-20, 20-2). We estimated the association of BMI with a diagnosis of stress fractures in male and female combat soldiers. We performed propensity score weighting among BMI groups and fitted a Kaplan-Meier model for each group. We used the Kaplan-Meier 1-year area under the curve and estimated the between-groups relative restricted mean time lost (rRMTL), with a higher value translated to increased incidence during the first year. The weighting model included demographics, medical history, enlistment year, and combat intensity (high and low).

Results:

We included 28,714 females and 164,333 males. During 513,220 person-years, stress fractures occurred in 4,166 (14.5%) females and 12,594 (7.7%) males. In 2014-2019 and 2020-2024 the respective incidences of stress fractures were 17.8% and 12.0% in females and 8.7% and 5.7% in males. Respective stress fracture incidence at high versus low combat-intensity was 23.7% versus 11.0% in females and 8.9% versus 4.9% in males. In females, compared with reference, the weighted stress fractures rRMTL was 1.17 (95% CI 1.10-1.25), 1.04 (0.98-1.10), 0.86 (0.81-0.92), and 0.54 (0.48-0.63) in individuals with BMI 18, 18-20, 25-32, and 32kg/m^2. The respective numbers among men were 1.25 (1.21-1.30), 1.16 (1.12-1.2), 0.90 (0.86-0.93), and 1.04 (0.98-1.09). There was no evidence that the association between BMI and incidence of stress fractures varied by combat intensity or recruitment year.

Conclusion:

Although the incidence of stress fractures decreased over the past decade, lower BMI was associated with a higher incidence of stress fractures among male and female combat soldiers. These findings indicate that low BMI can potentially serve as a marker of bone health even in young adults, with direct implications for combat allocation, and for development of strategies to prevent stress fractures during training and potentially osteoporosis at later adulthood.

199

Automated, Parallel Single-Nucleus RNA Sequencing of Multiple Pancreatic Islets from a NOD Mouse

Theophilus Ajiro[1], Anna Parnis[1], Nadav Sharon[1]
Faculty of Biology, Technion – Israel Institute of Technology, Haifa, Israel

Single-cell RNA sequencing (scRNA-seq) is an indispensable tool for profiling gene expression in heterogeneous tissues and is routinely applied to characterize pancreatic islet cell populations. Standard scRNA-seq workflows, however, require relatively large input material and cannot simultaneously capture inter-islet heterogeneity. Spatial transcriptomics partly addresses this limitation, but current platforms are costly, detect fewer genes per cell, and have limited ability to sample the full thickness of tissue sections.

Single-cell combinatorial indexing RNA sequencing (sci-RNA-seq) is a powerful alternative that relies on successive rounds of split-pool barcoding to uniquely label individual nuclei without physical cell isolation. This strategy enables sequencing of very large cell numbers at low cost. Because the method begins by distributing multiple cells across many wells, we reasoned that it could be adapted for parallel analysis of multiple samples from a Non obese Diabetic (NOD) mouse at the single cell level.

Here we describe an automated sci-RNA-seq workflow optimized for pancreatic islets. Our approach allows single-cell profiling of multiple small samples in parallel, revealing heterogeneity in cellular composition across islets. We programmed a robotic workstation to execute key library-preparation steps—including nuclei extraction and fixation, enzymatic reactions, split-pool barcoding, and final PCR amplification—thereby minimizing manual handling and shortening turnaround time. Additional refinements reduce nuclei loss during washes, enhance RNA stability, prevent genomic DNA contamination, and lower barcoding errors.

In summary, we present an enhanced, automated sci-RNA-seq protocol that preserves both cellular- and cluster-level information, yields high-quality libraries from small samples, and substantially reduces operator workload and processing time

200

Fib-4 Index Predicts Chronic Kidney Disease

Viviana Ostrovsky[1], Hilla Knobler[2], Arad Dotan[3], Saghi Tshori[4], Shay Ben- Haim[5], Taiba Zornitzki[1]

[1]*Hebrew University of Jerusalem, the Faculty of Medicine, Israel., Diabetes, Endocrinology and Metabolic Disease Institute, Kaplan Medical Center, Rehovot, Israel.*

[2]*Hebrew University of Jerusalem, the Faculty of Medicine, Israel, Diabetes Institute, Meuhedet HMO, Israel*

[3]*The Faculty of Medicine, Tel Aviv University, Israel, Sheba Medical Center, Ramat Gan, Isreal*

[4]*Hebrew University of Jerusalem, the Faculty of Medicine, Israel, Heart Institute, Kaplan Medical Center, Rehovot, Israel.*

[5]*Hebrew University of Jerusalem, the Faculty of Medicine, Israel., Braun School of Public Health and Community Medicine. The Hebrew University and Hadassah Medical Center*

Introduction: Metabolic dysfunction-associated steatotic fatty liver disease (MASLD) is the most common cause of chronic liver disease affecting up to 38% of adult population worldwide. MASLD is closely associated with cardio-metabolic disorders, which are also known to have a major role in the development of chronic kidney disease (CKD). However, the relationship between MASLD and CKD has been less investigated.

Objectives: To assess in a large cohort of adult men and women, with a wide range of age, metabolic status and comorbidities, whether FIB-4 index, a non-invasive tool for the prediction of liver fibrosis, can predict the development of CKD, in a long-term follow-up.

Methods: A retrospective cohort study based on database from Clalit Health Services between 2006 to 2023. The FIB-4 was calculated using the following formula: age (years)× AST (U/L)/(PLT [10^9/L]×ALT1/2 (U/L). The results were stratified to low (1.3), indeterminate (1.3 -2.67) and high (2.67) risk to develop fibrosis. CKD was defined eGFR 30 ml/min/1.73 m2, creatinine doubling, progression to end-stage renal disease (ESRD) or dialysis.

Results: A total of 329,699 individuals were included in the analysis. Of these, 225,537 (68.4%) were categorized as low-FIB-4 risk, 100,325 (30.4%) as indeterminate-risk and 3,837 (1.2%) as high-risk. Baseline mean eGFR was 94 ml/min/1.73 m2. Patients with eGFR 30 ml/min/1.73 m2, dialysis treatment and ESRD were excluded. The mean age at baseline was 56.6±4.7 years, with participants in the high-risk category being older 58.6±4.7 vs. 55.8±4.6 in the low-risk group (p0.001). During follow-up of 17 years 5,422 individuals (1.6%) developed CKD. The incidence of CKD increased across FIB-4 strata, from 1.6% in the low-risk group to 1.7% in the indeterminate group and 3.1% in the high-risk group (p0.001). A multivariable Cox regression analyses adjusted for sex, cardiovascular disease (CVD), smoking status, diabetes, hypertension, and statin use, found that higher FIB-4 was independently associated with an increased risk of incident CKD. Compared with the low-risk group, individuals in the indeterminate-risk category had a hazard ratio (HR) of 1.045 (95% CI, 0.986–1.108; p=0.135), and those in the high-risk category a HR of 1.749 (95% CI, 1.457–2.098; p0.0001).

Conclusion: A significant association was found between the incidence of CKD and high-risk FIB-4 index in this long-term follow up study. This association remained consistent across all subgroups and was independent of CVD and CVD risk factors. Our results imply that high FIB-4 index can identify long-term kidney function decline

203

A Temporal Map of Autoimmune Diabetes Progression Based on RNA Sequencing of Single Islets Reveals Distinct Patterns of Islet Deterioration

Tsofiya Szanton[1], Nadav Sharon[1], Paraskevas Filippidis[2], Gur Yaari[2]
[1]*Faculty of Biology, Technion*
[2]*Department of Pathology, Yale School of Medicine*

Type 1 diabetes (T1D) is an autoimmune disease characterized by destruction of insulin-producing β-cells. In both humans and the Non-Obese Diabetic (NOD) mouse model, immune infiltration develops heterogeneously across islets- while some islets remain intact, others develop insulitic lesions. A subset of these lesions has characteristics of Tertiary Lymphoid Organs (TLOs), known from various types of inflammation to function as sites of local immune activation. This raises the possibility that lymphocyte activation occurs within islets, rather than exclusively in secondary lymphoid organs.

To elucidate the role of insulitic TLOs in T1D progression, we aimed to construct a detailed map describing T1D progression at the single islet level, and the interactions between different islets within the pancreas. To this end, we developed a high-throughput protocol for joint transcriptome and immune repertoire (T- and B-cell receptor– TCR, BCR respectively) sequencing at the single-islet level, enabling integrated profiling of pancreatic islet states and lymphocyte clonality.

Concomitant sequencing of dozens of single islets from a single pre-diabetic NOD mouse allowed generation of paired transcriptomic and immune repertoire datasets, and construction of a pseudo-temporal trajectory spanning from lightly infiltrated islets to heavily infiltrated, beta cell deficient islets in the latter.

Preliminary analysis reveals substantial increase B cell markers in the islets as the attack unfolds, leading to the identification of two types of islets. The first is characterized by the appearance of TLOs, as deduced from expression of high endothelial venule markers. The other type of islet, although rich in B cell infiltration, shows no sign of TLO formation. Notably, both islet types present lower expression of beta cell markers, which may indicate beta cell loss. However, non-TLO islets present a decline in expression levels of all endocrine genes, including Gcg, Sst and Ppy, which suggests overall islet deterioration. Accordingly, histological analysis of a patient with early onset T1D reveals downregulation of CHGA across all cells in insulin deficient islets.

Together, these findings suggest that the autoimmune attack in T1D affects the entire islet, even though β-cells are selectively eliminated. Moreover, the identification of distinct islet states underscores the need to determine whether immune attacks across islets occur in a coordinated or disorganized manner. Analysis of BCR and TCR sequence dispersion—particularly BCR somatic hypermutation patterns—will provide insight into how autoimmune responses spread between islets. Overall, single-islet profiling captures the T1D progression and implicates TLOs as potential hubs of local clonal immune activation.

204

Early Hypocortisolism with Persistent Remission Following Osilodrostat Therapy in a Patient with Long-Standing Cushing Disease

Liat Sasson[1,2], Ilan Shimon[1,2]
[1]*Institute of Endocrinology, Rabin Medical Center, Beilinson Hospital*
[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

Background: Cushing syndrome is a disorder of endogenous hypercortisolism associated with increased morbidity and mortality, requiring effective long-term control of cortisol excess. When pituitary surgery is not feasible or unsuccessful, medical therapy targeting either adrenocorticotropic hormone (ACTH) secretion or adrenal steroidogenesis is commonly employed. Osilodrostat, a potent oral 11β-hydroxylase inhibitor, has emerged as an effective treatment.

Case Presentation: We present a 70-year-old woman with ACTH-dependent Cushing disease due to a pituitary macroadenoma (15 mm), diagnosed in 2008. The patient declined surgery and was managed medically for many years with pasireotide, resulting in marked tumor shrinkage (4 mm), and later combination therapy with metyrapone due to persistent hypercortisolism. Despite partial biochemical control, urinary free cortisol (UFC) remained elevated, prompting initiation of osilodrostat (2 mg twice daily) in February 2024, with discontinuation of metyrapone.

Within ten days of treatment initiation, the patient developed fatigue, nausea and hypotension. Morning serum cortisol was markedly low (76 nmol/L), consistent with adrenal insufficiency. Osilodrostat was immediately discontinued, and physiologic glucocorticoid replacement was initiated, with rapid clinical improvement.

Outcome and Follow-Up: Despite minimal exposure to osilodrostat, the patient developed sustained cortisol suppression. UFC normalized within approximately five weeks and remained within the normal range throughout nearly two years of follow-up without further Cushing-directed therapy. Morning cortisol levels demonstrated slow and incomplete recovery. A follow-up ACTH measurement revealed elevated ACTH in the presence of low-normal cortisol, suggesting impaired adrenal responsiveness after prolonged ACTH suppression. Clinically, the patient experienced substantial metabolic improvement, including a 16.5-kg weight loss and marked improvement in glycemic control, allowing discontinuation of insulin and GLP-1 receptor agonist therapy.

Conclusion: This is among the earliest documented cases of osilodrostat-induced hypocortisolism with long sustained hormonal remission after treatment discontinuation. It highlights the importance of early monitoring and awareness that prolonged remission may occur in select patients after brief adrenal steroidogenesis inhibition.

206

The Impact of Meal Bolus Timing and Rescue Strategies with Advanced Hybrid Closed-Loop Systems

Maya Laron Hirsh[1], Noga Minsky[1], Andrea Benedetti[2], Roy Anirban[2], Benyamin Grossman[2], Ohad Cohen[2], Amir Tirosh[3]
[1]*Endocrinology, Diabetes and Metabolism, Sheba Medical Center*
[2]*Medtronic*
[3]*Endocrinology, Sheba Medical Center*

Background: Achieving optimal postprandial glucose control remains a significant challenge in T1D management. While prescribing guidelines generally recommend delivering rapid-acting insulin 10-20 minutes prior to meals, real-world adherence is low due to social disruptions and fear of hypoglycemia. The Medtronic MiniMed 780G™ is an advanced hybrid closed-loop (AHCL) system utilizing adaptive algorithms and autocorrection to mitigate glycemic excursions, potentially offering flexibility in bolus timing.

Aim: To evaluate the clinical impact of various meal bolus timing strategies and delayed rescue protocols on postprandial glycemic control using an AHCL system.

Methods: In this prospective, single-center study, 15 adults using MM780G participated in two phases and glycemic measures were assessed in the 4-hour post-prandial period. First, subjects underwent standardized 54g carbohydrate (CHO) meal challenges comparing four strategies: 10-minute pre-meal bolus, at-meal bolus, and a 50% reduced CHO announcement delivered at 30 or 60 minutes post-meal. Second, participants completed two-week at-home phase comparing at-meal versus pre-meal bolusing.

Results: Mean age was 44.6±13.3 years, (67% female), and baseline HbA1c was 6.8%±0.007%. At-meal bolus achieved comparable time in range (TIR) to pre-meal bolusing (82±22% vs. 77±22%, p=0.50) and similar postprandial peaks (189.9±42.9 vs. 177.8±55.5 mg/dL, p=0.35). However, pre-meal bolusing was associated with significantly higher rates of hypoglycemia compared to at-meal delivery (TBR

Conclusions: AHCL technology may effectively eliminate the clinical necessity for pre-meal bolusing, as at-meal delivery provides non-inferior glycemic control with superior safety regarding hypoglycemia. This shift in clinical practice could substantially alleviate the treatment burden and psychological distress associated with rigid bolus timing, ultimately improving adherence and quality of life for individuals with T1D.

Figure 1: Postprandial glycemic excursion after meal challenges comparing bolus timing strategies

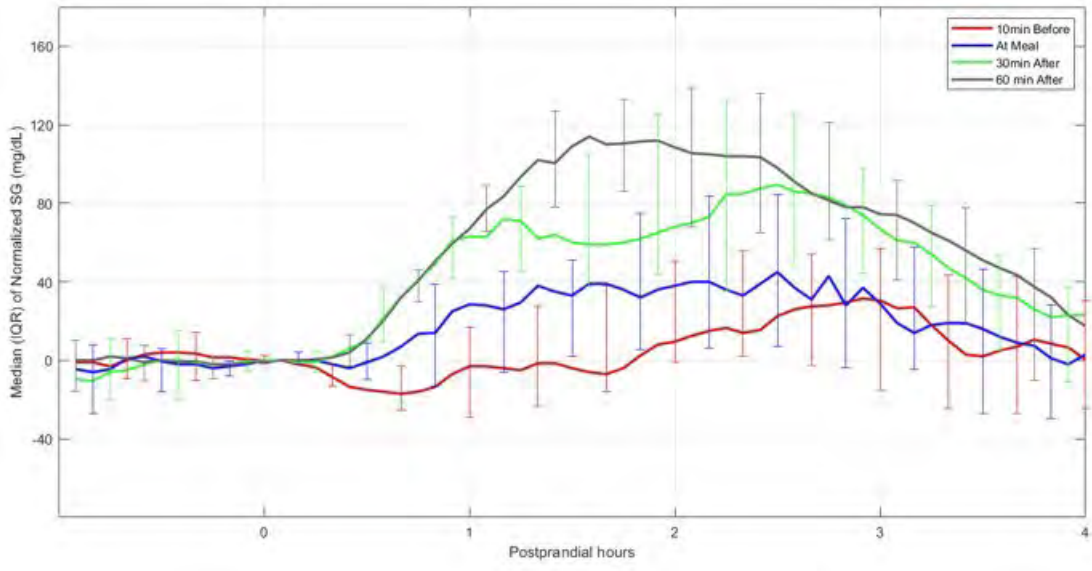
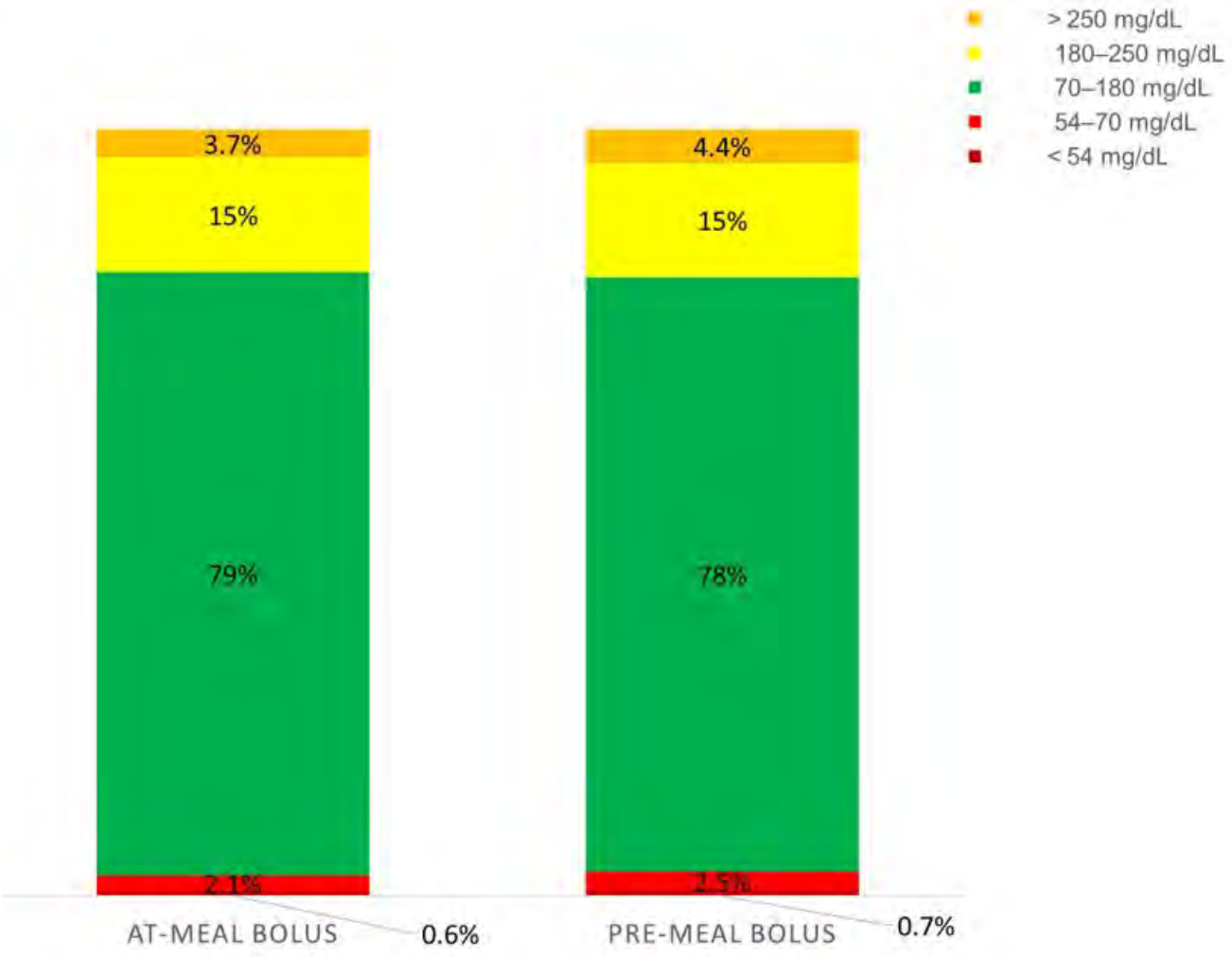


Figure 2. Time in different glycemic ranges for comparative at-home phases


> 250 mg/dL
180–250 mg/dL
70–180 mg/dL
54–70 mg/dL
< 54 mg/dL
3.7%
15%
79%
2.1%
AT-MEAL BOLUS
0.6%
4.4%
15%
78%
2.5%
PRE-MEAL BOLUS
0.7%

207

ProGRP as a biomarker in lung carcinoids associated with DIPNECH

Benjamin Nisman[1], **Anat Bel-Ange**[2], Ofra Maimon[3], Hovav Nechushtan[3], Nir Peled[4], Veronika Denysovaa[2], Simona Ben-Haim[5], Karin Atlan[6], Ori Wald[7], David Gross[2], Tamar Peretz[1], Simona Grozinsky-Glasberg[2]

[1]*Department of Oncology, Hadassah and Hebrew University Medical Center, Jerusalem, Israel*

[2]*Neuroendocrine Tumor Unit, ENETS Center of Excellence, Division of Internal Medicine, Hadassah Medical Center, Jerusalem, Israel*

[3]*Israel Sharett Institute of Oncology, Hadassah Medical Center, Jerusalem, Israel*

[4]*The Institute of Oncology, Shaarei Zedek Medical Center, Jerusalem, Israel, Jerusalem, Israel*

[5]*Department of Nuclear Medicine & Biophysics, Hadassah Medical Organization, Israel. Faculty of Medicine, Hebrew*

University of Jerusalem, Israel, Jerusalem, Israel

[6]*Department of Pathology, Hadassah Medical Organization, Jerusalem, Israel, Jerusalem, Israe*

[7]*Department of Cardiothoracic Surgery, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*

Introduction: Pulmonary carcinoids are neuroendocrine tumors comprising 1–2% of lung malignancies, treated primarily with surgery. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare preneoplastic condition often coexisting with carcinoids, lacking reliable biomarkers. Progastrin-releasing peptide (ProGRP) a marker of pulmonary neuroendocrine tumors, may serve as a diagnostic and monitoring tool. **Aim**(s): This study evaluated ProGRP for diagnosing carcinoids with concomitant DIPNECH, detecting residual disease after surgery, and monitoring treatment response. **Materials and methods**: ProGRP concentrations were measured in 43 patients with carcinoids and DIPNECH and in 105 with benign lung disease. Perioperative ProGRP was assessed in seven surgical patients. Thirty patients were monitored during follow-up: 10 after resection and 20 receiving somatostatin analogues, for a total of 114 samples. **Results:** ProGRP distinguished patients with carcinoids concomitant with DIPNECH (n=43) from those with benign lung disease (n=105): area under the curve 0.977 (p 0.0001); sensitivity 88.9%; specificity 95.2%; at 64 pg/mL. Perioperative measurements of ProGRP in seven patients revealed the significant associations of elevated levels after surgery with residual disease (in 6 of 7). ProGRP was monitored in 30 patients, including 10 pts after surgical resection as an observational surveillance and 20 patients treated with somatostatin analogues. Response Evaluation Criteria in Solid Tumors was used to define categories of response. Response to treatment categories (partial response [PR], stable disease, and PD) occurred in 10 (8.8%), 90 (78.9%), and 14 (12.3) cases, respectively. Receiver operating characteristic curve analysis was used to diagnose PR and PD by assessing dynamic ProGRP change during treatment. The AUCs were 0.965 (p 0.001) for detection of PR or PD, respectively. The optimal changes of ProGRP were a marker decrease of 28% for PR detection (sensitivity 80% and specificity 99.0%) and an increase of 29% for PD detection (sensitivity 79.0% and specificity 94%). **Conclusion:** ProGRP demonstrated excellent diagnostic accuracy in distinguishing carcinoids with DIPNECH from benign lung disease. Postoperative elevations identified residual disease, and dynamic ProGRP changes reliably reflected treatment response. ProGRP is an emerging biomarker with potential utility for diagnosis, postoperative surveillance, and response monitoring in patients with lung carcinoids and DIPNECH.

208

Distinct epigenetic aging in sporadic and hereditary neuroendocrine neoplasms

Shiri Weinstein[1,2], **Reut Halperin[2,3]**, Amit Tirosh[2,3]
[1]*Medicine D Ward, Sheba Medical Center*
[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*
[3]*ENTIRE– Endocrine Neoplasia Translational Research Center, Division for Endocrinology, Diabetes, and Metabolism, Sheba Medical Center*

Epigenetic clocks assess DNA aging based on DNA methylation. We aimed to study the utility of methylation clocks in understanding the distinct characteristics of sporadic and hereditary neuroendocrine neoplasms (NEN).

Methods

Epigenetic age and acceleration were calculated based on Horvath multi-tissue, Levine, and Hannum clocks, and compared by genetic predisposition and NEN grading (WHO-defined G1, G2, and G3).

Results

Following quality assessment and filtering of the data, 93/96 samples were analyzed. Of them, 41/93, 42/93, and 10/93 were sporadic, multiple endocrine neoplasia 1 (MEN1) and von Hippel-Lindau (VHL)-related NEN, respectively. Forty-eight (48/93) were pancreatic NEN (PNEN). mDNA age positively correlated with chronological age based on three different clock algorithms, but stronger correlations were found in the hereditary NEN subgroups (Horvath clock, r=0.65, p0.001 for MEN1-related NEN, and r=0.86, p=0.002 in VHL-related NEN). Epigenetic age acceleration was higher in sporadic NEN compared to hereditary NEN, both based on chronological age-adjusted epigenetic age (Hannum clock, sporadic vs. MEN, p=0.03; sporadic vs. VHL, p=0.0002), and based on the difference between epigenetic age and chronological age (Hannum clock, sporadic vs. MEN1, p=0.009; sporadic vs. VHL, p=0.0005). Finally, epigenetic age (p=0.04) and age acceleration (p=0.03) were higher among adult patients with NEN (G2/3 vs. G1).

Conclusions

Epigenetic age and age acceleration analysis demonstrate distinct patterns in sporadic and hereditary NEN, suggesting a lower impact of epigenetic alteration or DNA aging in the pathogenesis of hereditary NEN.

209

Diabetic retinopathy after liver transplantation: Impact of diabetes type

Keren Kaminer[1,2], Mor Atlas[3], Talia Diker-Cohen[1,2]
[1]*Rabin medical center, Petah Tikva, Israel*
[2]*Faculty of Medical and Health Sciences, Tel Aviv University, Israel*
[3]*Business Administration Faculty, Ono Academic College, Kiryat Ono, Israel*

Objective: Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus (DM). Among liver transplant recipients, DM may be present prior to transplantation or may develop post-transplant. Despite the well-recognized burden of diabetes in this population, data on the incidence, progression, and management of diabetic retinopathy after liver transplantation remain limited.

Design: A retrospective study of patients who underwent liver transplantation between 1996 and 2020 and were followed for at least one year post-transplantation in a tertiary referral center. All patients had no evidence of retinopathy at baseline.

Methods: Patients with less than one year of follow-up and/or without an ophthalmologic examination were excluded. Participants were classified into two groups according to diabetes type—type 2 diabetes mellitus (DM2) or new-onset diabetes after transplantation (NODAT)—and were assessed for diabetic retinopathy at baseline and at 1, 3, 5, 10, 15, 20, and 25 years following transplantation.

Results: Eighty-eight patients were included (mean age 53 ± 11 years; 33% female). Pre-transplant diabetes mellitus was present in 50% of patients, while the remaining 50% developed NODAT. Diabetic retinopathy developed in 13.6% of the cohort (n = 12). Patients who developed retinopathy had a higher prevalence of neuropathy (30% vs. 6.8%, p = 0.06) and hypertension (50% vs. 19.1%, p = 0.08) at baseline, as well as higher baseline HbA1c levels (8.6 ± 2.5 vs. 7.0 ± 2.3, p = 0.09). Patients with DM2 exhibited more than a sixfold increased risk of developing diabetic retinopathy during follow up compared with those with NODAT (HR = 6.527; 95% CI: 1.62–26.27; p = 0.008). Notably, retinopathy in patients with NODAT occurred only 15 years post-transplantation. The incidence rate of developing retinopathy was 1,600 per 100,000 person-years. When stratified by diabetes type, patients with NODAT had a markedly lower incidence rate (628 per 100,000 person-years) compared with those with pre-transplant diabetes (3,296 per 100,000 person-years).

Conclusion: In liver transplant recipients, the risk of developing diabetic retinopathy among patients with NODAT is low, with retinopathy occurring only after prolonged follow-up, beyond 15 years post-transplantation.

Higher Prevalence of Short Stature and Excess Weight in Children with Sleep Disorders.

Dr Inbal Halabi[1], Dana Hadar[2], Hilla Cohen[2], Yardena Tenenbaum Rakover[3], Giora Pillar[4]
[1]*Pediatric Endocrine Unit, Carmel Medical Center, Clalit Health Services*
[2]*Research Authority, Clalit Health Care Organization, Carmel Medical Center*
[3]*Children's Endocrinology Consulting Center, Clalit Health Services*
[4]*Sleep Clinic, Clalit Health Services, Technion Faculty of Medicine*

Background: Sleep disorders are common in childhood and are recognized as a significant public health concern, particularly due to their association with childhood obesity. However, their impact on growth disturbances has been only minimally explored.

Aim: In the present study, we investigate the association between sleep disorders and linear growth and excess weight in children.

Study Design: Data were collected retrospectively (January 2012–December 2022) from computerized medical records of 3,210 patients (newborn–18 years) diagnosed with sleep disorders who underwent sleep analysis at the Sleep Clinic of Carmel Medical Center. A control group (n =12,840), matched for age and ethnic background, was selected from the same healthcare database. Additionally, subgroup analyses were performed by sex and across three age groups.

Results: A higher rate of short stature, defined as height at or below the 3rd percentile, was observed in the study group compared to controls (8.66% vs. 6.25%, p 0.001). This difference was primarily seen in the 0–6 years age group (girls: OR 1.49, p = 0.003; boys: OR 1.57, p 0.001). The diagnosis of short stature and growth hormone deficiency was documented in 10.1% and 2.1% of the study group, respectively, compared to 7.5% and 1.15% in the control group (p 0.001 for both). Rates of overweight and obesity were higher among children in the study group compared to controls (overweight: 25.9% vs. 22.2%; obesity: 14.6% vs. 10.4%; p 0.001). This difference was primarily observed in children aged 6–18 years, with the strongest effects seen in adolescent boys. Notably, children with obstructive sleep apnea had a significantly higher prevalence of short stature compared to those with other sleep disorders (13.4% vs. 7.7%; p 0.001).

Conclusions: Our findings of a higher prevalence of growth disturbances and excess weight among children with sleep disorders highlight the importance of early recognition and timely intervention for pediatric sleep disorders. Such measures may improve sleep quality and daily functioning and potentially benefit growth and weight outcomes.

213

When Weight Loss Unmasks a Childhood Disease: Late Adult Presentation of Nesidioblastosis.

Esther Osher[1,2], Yael Sofer[1,2], Merav Serebro[1,2], Yoav Eizenberg[3], Yona Greenman[1,2], Michal Yacobi-Bach[1,2]

[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center*

[2]*Gray Faculty of Medical and Health Sciences, Tel-Aviv University*

[3]*Endocrinology and Diabetes unit, Clalit Health Service, Migdal HaMea Tel Aviv.*

Nesidioblastosis is typically diagnosed in infancy, whereas adult presentation is rare and may remain clinically silent for decades. Only a limited number of isolated case reports have described adult-onset nesidioblastosis.

Case: We report a case of late adult manifestation of nesidioblastosis in a 63-year-old woman, in whom clinically significant hypoglycemia emerged only after the development of prediabetes and intentional weight loss. The patient experienced episodes of seizure event treated by Phenytoin suggestive of hypoglycemia in early childhood, which resolved and were not documented for several decades. Throughout most of adult life, she had no clinically significant hypoglycemia. In her early sixties, she was diagnosed with prediabetes and initiated dietary modification, resulting in an intentional weight loss of approximately 10 kg. Following weight reduction, she developed recurrent fasting hypoglycemic episodes with neuroglycopenic symptoms.

Biochemical evaluation during spontaneous hypoglycemia demonstrated inappropriately detectable insulin and C-peptide levels, confirming endogenous hyperinsulinemic hypoglycemia, insulin autoantibodies were negative. Imaging, including multiphasic computed tomography and endoscopic ultrasound, failed to identify focal pancreatic lesions. Continuous glucose monitoring revealed recurrent fasting hypoglycemia, often asymptomatic.

Genetic testing identified compound heterozygous pathogenic variants in the ABCC8 gene, supporting a diagnosis of congenital hyperinsulinism with late adult reactivation of nesidioblastosis. Management included dietary modification with frequent complex-carbohydrate meals, nocturnal cornstarch supplementation, glucose monitoring, and consideration of diazoxide therapy.

Conclusion: This case highlights that nesidioblastosis may remain quiescent for decades and become clinically apparent following metabolic changes such as prediabetes and significant weight loss. Awareness of this trigger is essential to avoid misdiagnosis and unnecessary pancreatic surgery in adults presenting with hyperinsulinemic hypoglycemia.

Iron Supplementation and Stress Fractures Risk in 2910 Propensity-Score Matched Female Combatants with Low Ferritin Without Anemia

Noa Sofer Sali[1], May Merav[1,2], Hadar Sharvit[2]
[1]*IDF*
[2]*The Hebrew University of Jerusalem*

Background:

Stress fractures (SF) are a significant concern among female combatants and elite athletes. Anemia, common in this population, has been associated with an increased risk of fractures. It remains unclear whether this increased risk extends to individuals with iron deficiency without anemia, or whether iron supplementation modifies it. This raises a practical question: should iron supplementation, which can cause noticeable adverse effects, be recommended for these individuals when asymptomatic to reduce the risk of SF? Israeli Defense Forces (IDF) female combatants undergo anemia screening following enlistment. This screen provides a unique opportunity to investigate whether iron supplementation is associated with reduced SF risk among female combatants with iron deficiency without anemia.

Methods:

In a retrospective cohort study, using the IDF medical and administrative electronic record, we included female combat recruits (2014-2024) with blood hemoglobin 12 g/dL and plasma ferritin 15 ng/mL within 45 days of enlistment. Recruits with SF or Celiac disease before index date were excluded. We propensity score-matched (1:2) combatants that dispensed ≥60 or 60 iron supplementation tablets within 90 days of enlistment. We used Kaplan-Meier and Cox models to compare the groups for the incidence of SF diagnosis, defined by verified clinical protocols, after day 90 (index date). Analyses were repeated in subgroups defined by ferritin levels (5.0–7.5 and ≥7.5ng/mL), training intensity (high and low, pending role assignment), and enlistment years (2014–2020 and 2020–2024).

Results:

After propensity score matching, the cohorts comprised 970 and 1,940 individuals in the ≥60- and 60-tablet groups, respectively. We did not find evidence of a difference in the risk of SF in those dispensing ≥60 versus 60 iron supplementation tablets (HR = 0.91 [95% CI: 0.73-1.12]; figure). The between-groups HRs among the high- and low-ferritin-level categories were 0.91 [0.71-1.16] and 0.95 [0.62-1.44], respectively (p-interaction = 0.87). The respective HRs among those assigned to high and low training intensity were 0.94 [0.69-1.28] and 0.88 [0.65-1.18], and among those recruited in 2014-2020 and 2020-2024 were 1.05 [0.79-1.4] and 0.73 [0.53-1.01].

Conclusions:

In a nationwide cohort of 2910 propensity-score matched female combatants with low ferritin without anemia, there was no evidence that iron supplementation was associated with a reduced risk of SF after the first 90 days of enlistment. Further research is warranted to assess the potential effect of pre-training iron treatment on SF and other outcomes in this population.

217

RNA Editing Deficiency in Mouse Beta Cells Recapitulates Key Features of T1D Independently of Autoimmunity

Jonathan Belin[1], Udi Ehud Knebel[1], Shani Peleg[1], Maya Israeli[1], Miri Stolovich-Rain[1], Alvin C. Powers[2,3], Chunhua Dai[2], Heather R. Kates[4], Clive H. Wasserfall[4], MacKenzie Williams[4], Ann Fu[4], Martha Campbell-Thompson[4], Desmond A. Schatz[4], Benjamin Glaser[5], Erez Y. Levanon[6], Agnes Klochendler[1], Yuval Dor[1]

[1]*The Hebrew University of Jerusalem, Jerusalem, Israel*
[2]*Vanderbilt University Medical Center, Nashville, TN, US*
[3]*VA Tennessee Valley Healthcare, Nashville, TN, USA*
[4]*College of Medicine, University of Florida, Gainesville, FL, USA*
[5]*Hadassah Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel*
[6]*Bar-Ilan University, Ramat Gan, Israel*

An antiviral type-I interferon (IFN-I) response to double stranded (ds)RNA is implicated in early stages of type-1 diabetes (T1D), but evidence for a causal viral infection is limited. Endogenous RNA species, potentially retroelements, represent an alternative source for dsRNA, normally edited by the ADAR enzyme to prevent aberrant antiviral responses. It was recently suggested that this process is disrupted in autoimmune and autoinflammatory conditions, including T1D. Consistently, knockout of ADAR in mouse beta cells (beta-AdarKO) induced a robust IFN-I response and islet inflammation (insulitis), beta cell loss of identity preceding their selective elimination and diabetes, thereby mimicking key features of human T1D.

In this study we have characterized insulitis composition and assessed the importance of innate versus adaptive immunity in beta-AdarKO mice.

Immunohistochemistry revealed islet inflammation dominated by myeloid cells, with T and scattered B-cells present. However, T-cells lacked the activation marker Granzyme B, and insulin autoantibodies were not detected in the plasma, suggesting that adaptive immune cells are bystanders in this model of diabetes. Consistently, T and B-cell deficiency achieved by crossing with RAG1 knockout mice did not affect insulitis development, diabetes incidence, beta cell loss of identity and selective beta-cell death.

Depletion of circulating monocytes using anti-CCR2 antibodies reduced the macrophage fraction in insulitic lesions by 50%. This suggests that infiltration by monocyte-derived macrophages and local expansion of tissue-resident macrophages equally contribute to insulitis. In contrast, anti-CSF1R antibodies, which target all mature macrophages, almost completely abolished insulitis.

These findings challenge the current paradigm which poses T-cells as essential drivers of beta-cell damage in T1D. Future research will explore whether macrophage depletion protects beta cells from damage and prevents diabetes in this model, providing novel mechanistic insights into the early innate immune events which drive T1D.

218

Comparative Effects of Anti-Osteoporotic Therapies on Mortality Following Hip Fracture: A Real-World Study

Omri Armoni[1], Itay Pansky[1], Dmitry Shklovsky[2], Uri Yoel[2,3], Merav Fraenkel[2,3]
[1]*Goldman School of Medicine, Faculty of Health Science, Ben-Gurion University of the Negev*
[2]*Endocrinology, Soroka University Medical Center*
[3]*Faculty of Health Science, Ben-Gurion University of the Negev*

Background
Osteoporotic hip fractures are associated with substantial morbidity and excess mortality. Although anti-osteoporotic medications reduce fracture risk, their association with post-fracture survival—particularly across different drug classes in real-world clinical practice—remains uncertain.

Methods
We conducted a retrospective cohort study using data extracted via the MDClone platform from Clalit Health Services. Patients aged ≥50 years who were hospitalized and surgically treated for a first osteoporotic hip fracture between 2012 and 2021 were included. Patients with malignancy, fractures related to motor vehicle accidents, periprosthetic fractures, or subtrochanteric fractures were excluded.

Post-discharge anti-osteoporotic treatment was identified using pharmacy purchase records and categorized as oral bisphosphonates, zoledronic acid, denosumab, or no treatment. A single medication purchase was sufficient to classify a patient as treated. Patients who received more than one class of anti-osteoporotic medication during follow-up were classified according to the last medication purchased.

Demographic, laboratory, and clinical data were collected, and comorbidity burden was assessed using the Charlson Comorbidity Index (CCI). The primary outcome was all-cause mortality within three years of the index hospitalization. Survival was assessed using Kaplan–Meier analysis, and associations between treatment category and mortality were evaluated using Cox proportional hazards models adjusted for age, sex, estimated glomerular filtration rate, CCI, and socioeconomic status.

Results
A total of 6,977 patients were included (mean age 80 ± 10 years; 65% female). Overall, 72% (n=5,081) had no documented anti-osteoporotic treatment following fracture, while 6.2% (n=432) received oral bisphosphonates, 9.1% (n=637) zoledronic acid, and 12.7% (n=827) denosumab. In multivariable Cox regression models, post-fracture treatment with oral bisphosphonates (HR 0.39, 95% CI 0.30–0.50), zoledronic acid (HR 0.36, 95% CI 0.28–0.45), and denosumab (HR 0.46, 95% CI 0.39–0.54) was independently associated with lower all-cause mortality compared with no treatment (all p 0.001). Higher socioeconomic status was also associated with reduced mortality risk (HR 0.76, 95% CI 0.67–0.87).

Conclusions
In this large real-world cohort of patients with a first osteoporotic hip fracture, initiation of anti-osteoporotic therapy after hip-fracture was independently associated with substantially lower all-cause mortality in the three years following the fracture, compared with no treatment. These findings support the potential survival benefit of post-fracture osteoporosis treatment and underscore the persistent treatment gap in this high-risk population.

219

Bilateral Adrenal Incidentalomas With Minimal Hormonal Activity Revealing Pheochromocytoma: A Diagnostic and Management Challenge

Alexandra Nathan Wisney[1], Jaydira Del Rivero[2], Liat Barzilay Yoseph[1], Miki Heifler[3], Pnina Rotman Pikielny[1,4]

[1]*Meir Medical Center, Kfar Saba, Israel, Institute of Endocrinology, Diabetes and Metabolism*

[2]*Developmental Therapeutics Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda USA*

[3]*Meir Medical Center, Kfar Saba, Israel, Department of Urology*

[4]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

Background:

Adrenal incidentalomas are increasingly detected with widespread imaging, and bilateral lesions pose diagnostic and management challenges. Although biochemical evaluation is central to risk stratification, pheochromocytomas may rarely demonstrate minimal or atypical biochemical abnormalities, delaying diagnosis.

Clinical Case:

A 62-year-old woman was incidentally found to have bilateral adrenal masses during abdominal imaging. Contrast-enhanced CT demonstrated a 3.3-cm HU 30 heterogeneous left adrenal mass with cystic and calcified components and a 2-cm HU 45 right adrenal lesion with similar imaging characteristics. Serial imaging over six months showed progressive left-sided growth, while the right-sided lesion remained stable, with minimal change on retrospective review dating back to 2007.

Comprehensive hormonal testing was unremarkable except for an isolated two-fold elevation in urinary dopamine levels, which was rendered insignificant and did not initially raise suspicion for pheochromocytoma. Due to radiologic concern and interval growth, the patient underwent robotic-assisted left adrenalectomy.

Histopathology confirmed pheochromocytoma. Postoperative staging, including whole-body MRI and PET-DOPA functional imaging, showed no metastatic disease; however, tracer uptake was noted in the remaining right adrenal gland. Subsequent genetic testing revealed a heterozygous SDHAF2 variant labeled as a VUS (variant of uncertain significance).

Conclusion:

This case highlights the diagnostic complexity of bilateral adrenal incidentalomas and demonstrates that pheochromocytoma may present with minimal biochemical abnormalities, including isolated dopamine elevation. Furthermore, the genetic result places the clinical team in a management dilemma: whether to recommend right-sided cortical-sparing adrenalectomy versus continued surveillance, given the lesion’s unchanged appearance on imaging over many years.

220

Breathing new life into gestational diabetes diagnosis: pilot study of a novel non-invasive breath test

Maya Oberman, Tal Schiller[1], Amir Shafat[2], Inbal Avrahami[3], Alena Kirzhner[3], Ziv Tsafrir[3], Edi Vaisbuch[3], Oren Barak[3]
[1]*Edith Wolfson Medical Center*
[2]*School of Pharmacy and Medical Sciences, University of Galway*
[3]*Kaplan Medical Center*

Objective

To evaluate the feasibility and diagnostic accuracy of exogenous glucose oxidation, as measured by an oral 13C-glucose breath test for diagnosing gestational diabetes mellitus (GDM).

Study Design

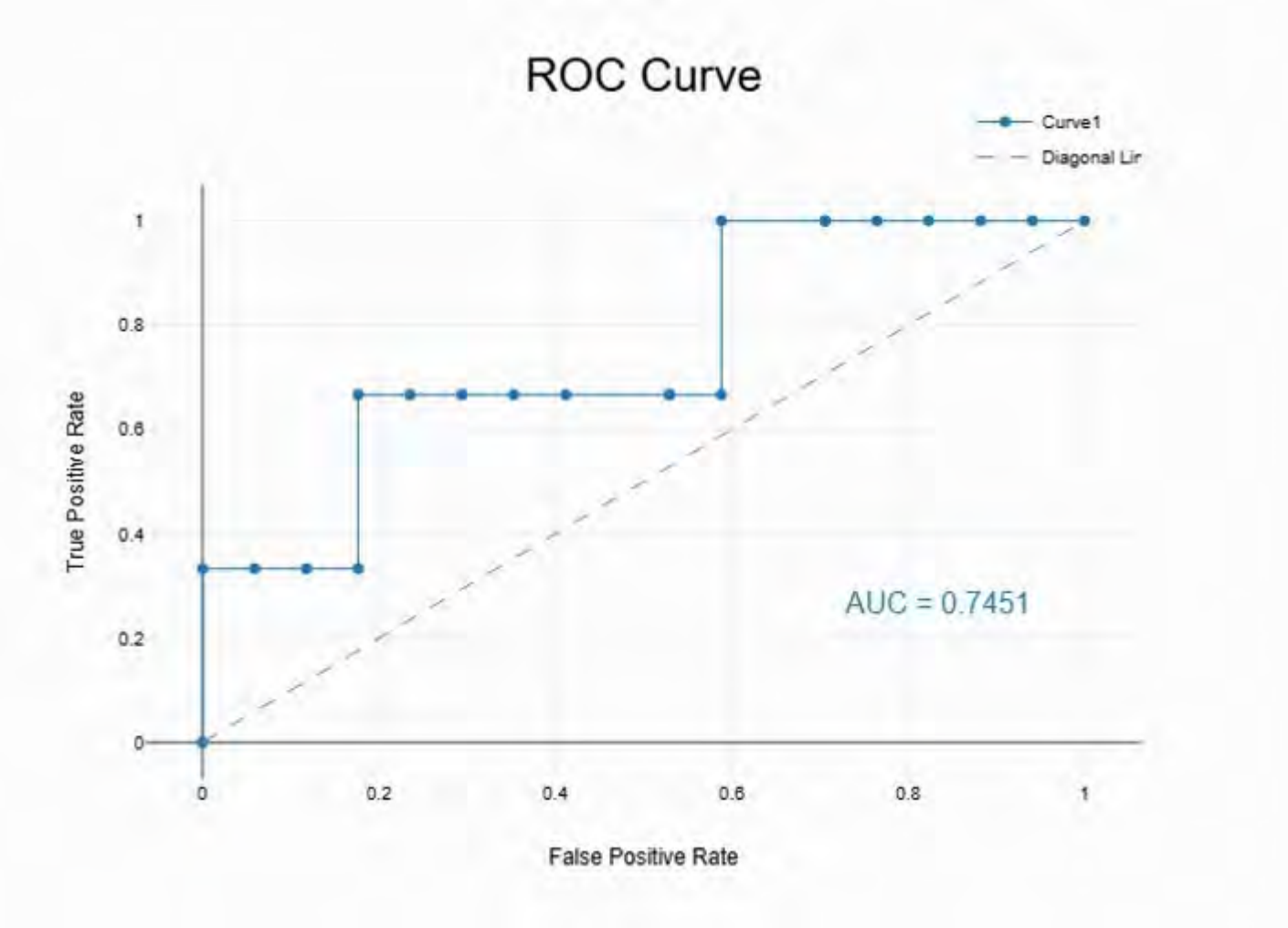
This single center prospective pilot study included individuals with singleton pregnancies scheduled for a 100-gram oral glucose tolerance test (OGTT) before 33 weeks' gestation. Participants ingested 100g 13C-labelled glucose after an overnight fast. Venous glucose was obtained before ingestion and 1, 2, and 3 hours after. GDM was diagnosed with ≥2 abnormal values. Breath samples were collected every 15 minutes for 3 hours and analyzed by GC-isotope-ratio mass spectrometry. Percent dose recovered (PDR) was calculated from the breath enrichment of 13CO2 multiplied by assumed CO2 production rates, so that the fraction of oxidized 13C-glucose (tracer) represented the fraction of the ingested glucose (tracee) metabolized to CO2. Feasibility outcomes were recruitment and test completion. Diagnostic accuracy was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). Pearson correlation coefficient was used to calculate the agreement between glycemia and exogenous glucose oxidation. The study protocol was approved by the institutional review board committee.

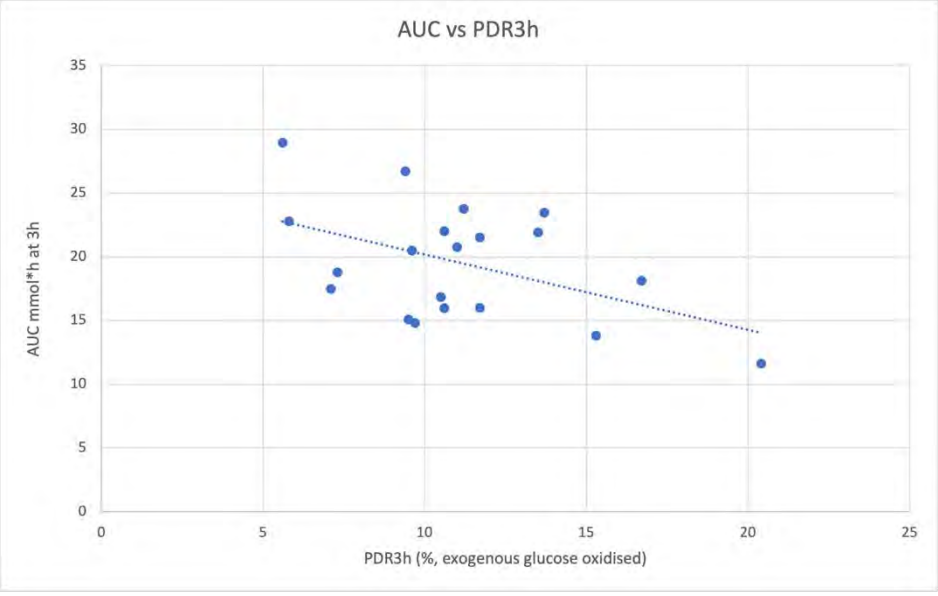
Results

All 20 participants completed 3 hours of breath-test sampling; no adverse events occurred. Patients diagnosed with GDM (n=3) had a lower, yet not reaching significance, median PDR at 3 hours (PDR3h) than in those without GDM [9.4 (7.5-10.3) vs 10.6 (9.6-13.5)]. PDR3h discriminated GDM with an AUC 0.75 (95 % CI 0.33-1.00), (Figure 1). A threshold of PDR3h 9.4% yielded 67% sensitivity and 82% specificity. PDR3h correlated inversely with OGTT glucose AUC ($r = -0.48$, $r^2 = 0.23$, $p = 0.03$), (Figure 2).

Conclusions

The 13C-glucose breath test was readily completed and allowed quantification of ingested glucose metabolism. PDR3h showed a moderate ability to identify GDM and was inversely correlated with OGTT. These findings support exploring this novel non-invasive diagnostic approach in larger cohorts.


ROC Curve
Curve1
Diagonal Lir
True Positive Rate
False Positive Rate
AUC = 0.7451
0
0.2
0.4
0.6
0.8
1


AUC vs PDR3h
AUC mmol*h at 3h
PDR3h (%, exogenous glucose oxidised)
0
5
10
15
20
25
30
35

221

Angiotensin 1-7 (Ang1-7) as a Potential Therapeutic Modulator of Skeletal Muscle Inflammation and Atrophy

yonit marcus[1,2], Gabi Shefer[1,3], Gilad Lehman[1], Yona Greenman[1,2], Naftali Stern[2,3]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel*
[2]*Faculty of Medicine, Tel Aviv University*
[3]*The Sagol Center for Epigenetics and Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel*

Background: Skeletal muscle dysfunction is a central feature of metabolic syndrome (MetSyn) and aging, contributing to insulin resistance, chronic inflammation, and progressive loss of muscle mass and function. Experimental and clinical evidence indicates that dysregulation of the renin–angiotensin–aldosterone system, particularly chronic overactivation of the angiotensin II (Ang II) pathway, adversely affects skeletal muscle. Ang II promotes muscle atrophy, inflammation, oxidative stress, and fibrotic remodeling via impaired insulin signaling, activation of proteolytic pathways, and induction of profibrotic cytokines, leading to reduced regenerative capacity and sarcopenia in metabolic disease and aging.

Objective: To investigate the effects of Angiotensin 1-7 (Ang1-7) on skeletal muscle atrophy, inflammation, regeneration, and structural integrity in experimental models of MetSyn and aging.

Methods: MetSyn was induced in rats using a fructose-fed diet (n=5, 6 months), alongside an aged cohorts (n=5, 17 months). Ang1-7 was administered by continuous infusion using Alzet mini-pumps. Gastrocnemius muscle was analyzed by quantitative real-time PCR for genes related to muscle atrophy, regeneration, inflammation, and calcium-dependent contraction. Muscle morphology was assessed by myofiber cross-sectional area (CSA).

Results: Young fructose-fed MetSyn and aged rats exhibited increased expression of the atrophy-related E3 ubiquitin ligases Atrogin-1 (MAFbx) and MuRF1 and the profibrotic cytokine TGF-β, alongside altered expression of regeneration-related genes (MyoD, Myogenin) and genes involved in calcium-dependent contraction. Molecular features consistent with impaired leptin responsiveness suggested skeletal muscle leptin resistance. Ang1-7 significantly downregulated Atrogin-1, MuRF1, and TGF-β, restored MyoD and Myogenin expression, normalized calcium-handling gene expression, and reduced long-chain fatty acyl-CoA ligase 4 (ACSL4), indicating improved lipid handling. These changes were associated with increased myofiber CSA in aged animals.

Conclusion: Ang1-7 protects skeletal muscle by suppressing atrophy and inflammatory signaling while promoting regeneration and structural maintenance, supporting its potential as a potential therapeutic target in MetSyn and aging.

222

Insulinoma and Pancreatic Hyperplasia After Bariatric Surgery

Yael Sofer[1,2], Dana Zaid[3], Yona Greenman[2,4], Esther Osher[2,4]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*
[3]*Institute of Endocrinology, Metabolism and Hypertension, Maccabi Healthcare Services*
[4]*Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

Hypoglycemia following bariatric surgery is increasingly recognized, with reported prevalence reaching up to more than 50% in some series. It is typically characterized by an exaggerated postprandial insulin response, while fasting glucose levels generally remain normal.

Case Report

A 49-year-old man presented with recurrent episodes of presyncope, dizziness, and confusion, which worsened after meals and physical activity. Three years earlier, he had undergone sleeve gastrectomy, initially losing 45 kg (from 155 kg to 110 kg) before regaining 10 kg. During symptomatic episodes, glucose levels were as low as 33 mg/dL. Despite treatment with liraglutide, semaglutide, and acarbose, his symptoms persisted. Continuous glucose monitoring revealed fasting hypoglycemia, raising suspicion for insulinoma. A brief fast (12 hours) resulted in a glucose level of 45 mg/dL, with concurrent insulin of 21 mIU/L and C-peptide of 4.23 ng/mL. A CT scan identified a 1.8 cm lesion in the pancreatic body. The patient underwent a distal pancreatectomy, with pathology confirming a 2 cm well-differentiated pancreatic neuroendocrine tumor (PNET) alongside focal β-cell hyperplasia.

Conclusion

The coexistence of PNET and β-cell hyperplasia is extremely rare, with approximately 21 cases reported in the literature. Its occurrence post-bariatric surgery is even more uncommon, with only four known cases. Clinicians should maintain a high index of suspicion for this entity when evaluating post-bariatric hypoglycemia, particularly in patients with fasting hypoglycemia.

223

δ-cell inhibition renews β-cells and insulin independence in diabetes

Yara Hamshawi[1], Nagham Gudban[1], Florin-Daniel Bîlbîe[2], Daljeet Kaur[1], Manar Hijazi[1], Yael Riahi[3], Offir Ertracht[4], Maria Naama[1], Rita Bottino[5], Assaf Malka[1], Shai Bel[1], Shaul Atar[4], Gil Leibowitz[3], Andrei Păun[6,7], **Ron Piran**[1]

[1]*The Azrieli Faculty of Medicine, Bar-Ilan University*

[2]*National Institute of Research and Development for Biological Sciences*

[3]*Faculty of Medicine, Hebrew University of Jerusalem*

[4]*Galilee Medical Center, Eliachar Research Laboratory*

[5]*Imagine Pharma*

[6]*ICUB/Faculty of Mathematics and Computer Science, University of Bucharest*

[7]*Research Institute for Artificial Intelligence, Romanian Academy*

The decline of functional insulin-secreting β-cells underlies all major forms of diabetes, yet effective approaches to promote their regeneration remain scarce. In this study, we report the experimental validation of a predictive framework indicating that suppression of somatostatin (Sst) expression enables endogenous β-cell regeneration with restoration of glucose responsiveness. Mice lacking Sst exhibited spontaneous recovery from chemically induced diabetes, demonstrating that removal of this inhibitory signal permits functional regeneration. Building on this observation, we identified cysteamine, an FDA-approved compound, as a pharmacological suppressor of Sst production in both murine and human primary islets. Reducing Sst levels relieved an inhibitory constraint on intrinsic regenerative programs within the endocrine pancreas. In wild-type diabetic mice, cysteamine recapitulated the regenerative phenotype observed in Sst-deficient animals. Notably, in autoimmune-prone NOD mice, treatment restored β-cell function and achieved insulin independence. Collectively, these results establish somatostatin downregulation as a central regulatory lever for β-cell regeneration and position cysteamine as a clinically viable candidate for regenerative therapy in diabetes.

224

Impact of Autoimmune Hypothyroidism and Celiac Disease on Progression to Diabetes in GAD- or IA-2 Positive Individuals

Afif Nakhleh[1,2], Naim Shehadeh[1,2]
[1]*Maccabi Healthcare Services, Haifa, Israel*
[2]*The Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel*

Introduction and Objective: Recent evidence suggests that the risk of developing autoimmune diabetes is higher in individuals with autoimmune hypothyroidism (AH) or celiac disease (CD). We aimed to assess whether a diagnosis of AH or CD influences the risk of progression to clinical diabetes among normoglycemic or dysglycemic individuals who tested positive for autoantibodies against glutamic acid decarboxylase (GAD) or islet antigen-2 (IA-2).

Methods: This retrospective cohort study utilized electronic health records from Maccabi Healthcare Services, Israel. We included individuals of all ages identified between January 1, 2010, and December 31, 2024, who had at least one positive autoantibody (GAD or IA-2). The index date was the first positive autoantibody test. Individuals diagnosed with diabetes within 3 months of the index date were excluded. AH was defined by ICD-9 codes plus positive thyroid peroxidase antibodies; CD was defined by ICD-9 codes. Follow-up concluded at diabetes diagnosis or September 30, 2025. Cox regression models, adjusted for age, sex, and socioeconomic status, estimated hazard ratios (HR) for incident diabetes.

Results: We analyzed 363 individuals (mean age 27.1 ± 18.4 years; 52.9% female), of whom 151 (41.6%) were dysglycemic at baseline. During a median follow-up of 5.8 years [IQR 2.2-9.4], 75 individuals (20.7%) developed diabetes, with a median time to diagnosis of 1.6 years [IQR 0.8-3.6]. Progression rates were 35.8% among dysglycemic versus 9.9% among normoglycemic individuals (P 0.001). At the end of follow-up, the prevalence of AH or CD was significantly higher in progressors versus non-progressors (21.3% vs. 10.4%; P = 0.01). The HR for incident diabetes was 2.23 (95% CI 1.27-3.91) for individuals with AH or CD compared to those without either. When analyzed separately, the HR was 3.10 (95% CI 1.32-7.28) for AH and 1.94 (95% CI 1.01-3.74) for CD.

Conclusion: In individuals with islet autoimmunity, concurrent AH or CD was independently associated with a higher risk of incident diabetes.

The Impact of Maternal Diabetes on Infantile Hemangioma: Evidence from a Large Population-Based Cohort

Nir Amitai[1], Eliya Honig[2]
[1]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[2]*Department of Obstetrics and Gynecology, Soroka medical center*

Background: Infantile hemangioma (IH) is the most common vascular tumor of infancy. While maternal metabolic conditions, particularly diabetes, may influence fetal vascular development, evidence on the association between maternal diabetes and IH remains inconsistent.

Objective: To assess the association between maternal diabetes—type 1 (DM1), type 2 (DM2), and gestational diabetes mellitus (GDM)— and IH incidence in offspring, considering antidiabetic medication use and maternal glycemic control.

Methods: We conducted a retrospective population-based cohort study using Clalit Health Services electronic health records, including 331,335 singleton live births from 2010 to 2023. Maternal diabetes status, treatment, and HbA1c levels were identified from ICD-10 codes and prescription records. The primary outcome was neonatal IH diagnosis. Logistic regression models adjusted for maternal and perinatal factors estimated odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Among 331,335 mother-child pairs, IH was diagnosed in 9,636 infants (2.9%). Incidence was higher among offspring of diabetic mothers (3.5%) versus non-diabetic mothers (2.9%, p 0.001). The strongest association was with maternal DM1 (4.7%, p 0.001). GDM also increased IH risk (3.4%, p 0.001), while DM2 showed a non-significant trend (3.4%, p = 0.061). Antidiabetic treatments (insulin, sulfonylurea, metformin) and maternal glycemic control (HbA1c ≥ 6.5%) were not associated with IH prevalence. In adjusted analyses, maternal diabetes remained an independent IH predictor (aOR 1.14, 95% CI 1.05–1.25, p = 0.003).

Conclusions: Maternal diabetes, specifically Type 1 and gestational diabetes, is independently associated with 14% higher odds of infantile hemangioma in offspring (aOR 1.14), regardless of glycemic control levels or pharmacological intervention.

227

Continuous Glucose Monitoring Metrics for Predicting Perinatal Outcomes in Women with Type 1 Diabetes Mellitus

Sarit Helman[1], Maayan Bas-Lando, Sorina Grisaru-Granovsky, Ofri Oren, **Orit Barenholz**[2]
[1]*Obstetrics and gynecology, Shaare Zedek medical center*
[2]*Obstetrics and gynecology, Laniado medical center*

Objective: Investigate the relationship between continuous glucose monitoring (CGM) derived glucose metrics, in each trimester, and the pregnancy outcomes in women with type 1 diabetes mellitus (T1DM).

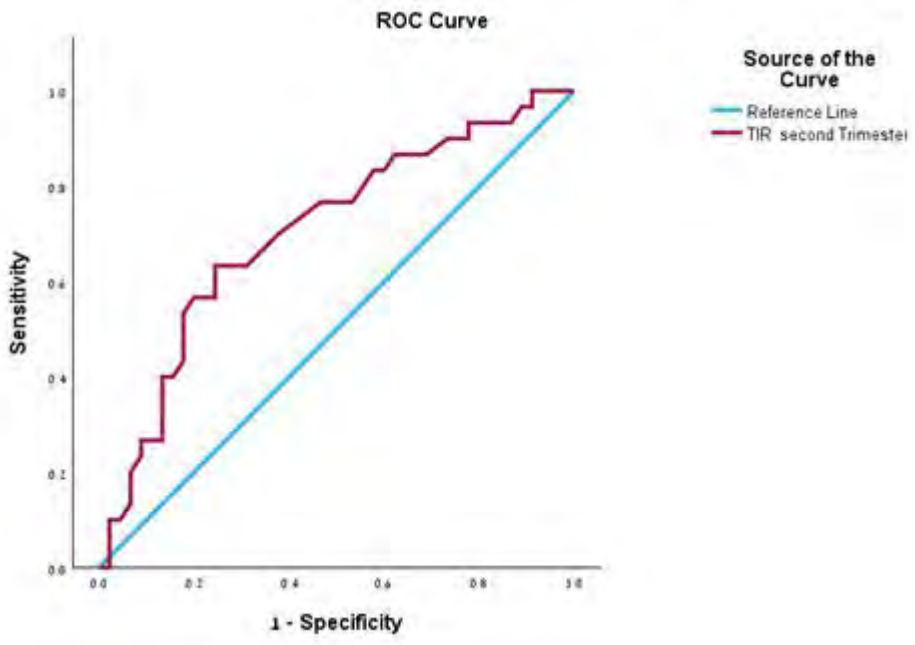
Methods: A retrospective cohort study (2020–2025) compared CGM metrics between women with T1DM who experienced pregnancy complications and those with uncomplicated deliveries. The primary outcome was large for gestational age (LGA); the secondary outcome was a composite of pregnancy complications. Associations with outcomes were evaluated using binary and multivariable logistic regression, including stepwise models (95% CI). ROC curves were constructed for metrics significantly associated with the primary outcome.

Results: CGM data were analyzed from 88 women; 32 (36.4%) delivered LGA infants and 56 (63.6%) did not. Women with LGA outcomes had higher mean glucose levels and lower time in range (TIR) across all three trimesters. Higher glucose standard deviation (SD) and greater time above range (TAR) during the second trimester were also significantly associated with LGA. TIR across all trimesters was associated with the secondary outcome. Second-trimester TIR was the strongest predictor of LGA, with each 5% increase in TIR associated with a 35% reduction in risk (OR 0.65, P0.05). A TIR threshold of ≥60% optimally discriminated LGA risk, with sensitivity 0.75 and specificity 0.63.

Conclusion: Higher CGM TIR during pregnancy was associated with lower LGA risk, with second-trimester TIR showing the strongest predictive value. These findings suggest that the second trimester may be a window of opportunity for interventions to improve glycemic control and potentially reduce LGA risk.

Figure 1

Receiver operating characteristic (ROC) curve for association of second trimester's TIR with LGA.



228

SGLT2 Inhibitor–Associated Ketoacidosis in a Non-Diabetic Patient with Duchenne Muscular Dystrophy

Gavriel Lichewitz[1], Gabriel Munter[1], Noa Sylvetzky[1], Dor Eldar[1], Michal Manovich[1], Meir Frankel[1]

Endocrinology unit, affiliated to Faculty of Medicine, Hebrew University, Shaare Zedek Medical Center, Jerusalem, Israel

Non-diabetic ketoacidosis is an uncommon but potentially life-threatening metabolic condition characterized by ketone body accumulation and metabolic acidosis in the absence of diabetes mellitus. Although rare in the general population, ketoacidosis has been reported as a metabolic complication in patients with Duchenne muscular dystrophy, particularly during periods of fasting or acute illness. We report the case of a 23-year-old non-diabetic male with advanced Duchenne muscular dystrophy and cardiomyopathy who developed ketoacidosis while receiving dapagliflozin, which had been initiated for heart failure a few weeks prior. This episode of ketoacidosis was precipitated by a near-complete cessation of oral food and fluid intake for two days prior to hospital admission, secondary to severe gastrointestinal dysmotility.

On presentation, laboratory evaluation revealed high anion-gap metabolic acidosis with markedly elevated serum ketone levels and normoglycemia. Discontinuation of dapagliflozin, together with intravenous administration of dextrose and bicarbonate, resulted in complete clinical and biochemical resolution without the need for insulin therapy.

To date, only a limited number of cases of SGLT2 inhibitor (SGLT2i)–associated ketoacidosis have been reported in non-diabetic patients. To our knowledge, this represents the third reported case of ketoacidosis in a non-diabetic patient with Duchenne muscular dystrophy receiving an SGLT2i. In this context, ketoacidosis likely results from the combined effects of SGLT2i-induced metabolic changes and the profound skeletal muscle involvement inherent to Duchenne muscular dystrophy, which significantly impairs gluconeogenic capacity during fasting and promotes an early shift toward lipolysis and ketogenesis, even in the absence of hyperglycemia.

In conclusion, SGLT2 inhibitors should be used with caution in patients with Duchenne muscular dystrophy, even in non-diabetic patients, particularly during periods of reduced caloric intake or acute illness, given the increased risk of ketoacidosis in this vulnerable population.

229

Predictors of Adverse Outcomes in Diabetic Patients Hospitalized with Acute Decompensated Heart Failure

Sheli Rivman[1], Tal Schiller[2,3], Hefziba Green[1,4], Haitham Abu Khadija[1,5], Joshua Friedman[1,4], Ilona Hrechkan[1,4], Saher Jammal[1,4,6], **Alena Kirzhner**[1,4]

[1]*Faculty of Medicine, The Hebrew University of Jerusalem*

[2]*Institute of Endocrinology, Diabetes and Metabolic Disease, Wolfson Medical Center*

[3]*Gray Faculty of Medical and Health Sciences, Tel Aviv University*

[4]*Department of Internal Medicine A, Kaplan Medical Center*

[5]*Department of Cardiology, Kaplan Medical Center*

[6]*Institute of Pulmonology, Kaplan Medical Center*

Background: Diabetes is highly prevalent among patients hospitalized with acute decompensated heart failure (ADHF), yet its prognostic impact remains uncertain. The emergence of cardio-protective therapies in recent years may influence outcomes. This study aimed to identify predictors of one-year all-cause mortality among diabetic patients hospitalized with ADHF in an internal medicine department.

Methods: This single-center retrospective cohort study included consecutive patients hospitalized with a primary diagnosis of ADHF in Internal Medicine Department A at Kaplan Medical Center between January 2020 and December 2023. Only the first hospitalization was analyzed. Patients were followed for 12 months and stratified into diabetic and non-diabetic groups. Data on demographics, laboratory values, comorbidities, echocardiography, chronic medications, and clinical outcomes, including length of stay, in-hospital mortality, one-year mortality, and rehospitalizations, were collected. Predictors of one-year mortality among diabetic patients were assessed using multivariable logistic regression.

Results: The cohort included 410 patients (mean age 76 ± 9 years, 49% men, BMI 30 ± 6 kg/m²); Approximately 70% had ejection fraction 40%. Diabetes was present in 238 patients (58%). Diabetic patients were younger, had higher BMI, and more often had hyperlipidemia, chronic kidney disease, and ischemic heart disease. Use of contemporary chronic therapies was low: 4% received sacubitril–valsartan, 14% SGLT2 inhibitors (21% of diabetics), and 7% GLP-1 receptor agonists (11% of diabetics). Outcomes were similar between groups, with ~9% in-hospital mortality, 25% one-year mortality, and nearly 50% heart-failure rehospitalization. Length of stay was significantly longer in diabetics (6 ± 7 vs 5 ± 5 days, p=0.036). In diabetics, older age and higher admission uric acid were identified as independent predictors of one-year mortality.

Conclusion: Diabetes was common and associated with longer hospitalization. Despite similar mortality and rehospitalization rates between groups, low use of contemporary disease-modifying therapies highlights an important opportunity to improve outcomes in this high-risk population.

230

High Prevalence of Poor Sleep and Psychological Distress in a Transgender Clinic Cohort: A Cross-Sectional Study.

Iris Yais[1], Rivi Tauman[2], Jennifer Zitser Koren[2], Yona Greenman[1]
[1]*Endocrine Institute, Tel Aviv Sourasky Medical Center (Ichilov) and Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[2]*Sieratzki Sagol institute for Sleep Medicine, TASMC*

Background/Introduction: Transgender individuals experience minority stress and frequently use gender-affirming hormone therapy, factors that may influence sleep and mental health. Sleep disturbance profiles in transgender men and women are understudied. We assessed the burden of poor sleep and psychological symptoms in a tertiary transgender clinic cohort.

Methods: Adults (≥18 years) consecutively attending the Transgender Clinic at Tel Aviv Sourasky Medical Center completed questionnaires on demographics, comorbidities/medications, health behaviors and hormone-therapy status. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) and OSA risk with STOP-BANG. Depressive symptoms, anxiety and perceived stress were assessed with BDI, GAD-7 and PSS. Groups were compared using chi-square and nonparametric tests.

Results: Of 174 participants (56% transgender women), median age was 23 years (IQR 19–29) and median BMI 23.0 kg/m² (IQR 20.6–27.1); 55% reported current hormone therapy. Overall, 63% had poor sleep (PSQI5; median PSQI 7 [IQR 5–10]) and 7% reported snoring. Clinically significant depression (BDI14) was present in 7%; anxiety was common (36% mild, 17% moderate, 16% severe) and stress was elevated (58% moderate, 12% high). Compared with transgender women, transgender men had higher rates of poor sleep (72% vs 55.6%, p=0.043), depression (14% vs 2.1%, p=0.003), severe anxiety (25.7% vs 9.2%, p=0.001) and moderate–high stress (81.5% vs 61.8%, p=0.012).

Conclusion: Poor sleep and psychological distress are highly prevalent among transgender adults, with a disproportionate burden in transgender men. Integrating routine sleep and mental health screening into transgender care may enable earlier, targeted interventions.

231

The effect of sex hormone priming on LHRH test results

Ilana Koren[1,2], Majd Abu Raia[2], Shadi Ibrahim[3], Hussein Majdoub[3], Inbal Halabi[3], Keren Cohen[3], Shira London[3], Hannah Ludar[3]

[1]*Pediatric Endocrinology Unit, Carmel Medical Center, Clalit Health Services*

[2]*Rappaport Faculty of Medicine, Technion-Israel Institute of Technology*

[3]*Pediatric department , Carmel Medical Center, Clalit Health Services*

Introduction

The diagnosis of short stature in children includes a growth hormone stimulation test in order to diagnose growth hormone deficiency In children without advanced puberty in the age in which it is expected, it is required to give preparation by administering sex hormones (priming) before performing growth hormone stimulation test. When pubertal assessment is also required, LHRH (Luteinizing Hormone Releasing Hormone) test is performed mostly seperately, as priming is considered to suppress gonadotropin levels.

. .

Aim

To examine whether administering sex hormones as a preparation before performing the growth hormone stimulation test affects the results of the puberty test (LHRH test).

Methods

This was a retrospective study, which examined the files of children who were under endocrine follow-up due to short stature at the pediatric endocrine unit at Carmel Medical Center between January 2000 and September 2024, and underwent both a growth hormone stimulation test and LHRH test on the same day and also underwent a preparation for the growth hormone test with sex hormones. The control group included children that underwent both a growth hormone stimulation test and LHRH test on the same day without preparation for the growth hormone stimulation test with sex hormones. LH value greater than or equal to 5 mIU/L was considered pubertal.

Data analysis was done using IBM statistics vs. 24.0 (SPSS). P

Results

This study included 103 children. 85 children underwent preparation with sex hormones (priming) followed by a growth hormone stimulation test and a puberty test (LHRH) on the same day. 59 of 85 children who underwent sex hormone preparation (69.4%) had a pubertal LH value, compared to 8 of 18 children who did not undergo priming (44.4%). The median LH values in the priming group were 7.1 mIU/L at time 30, 6.2 mIU/L at time 60, and 5.2 mIU/L at time 90.

Conclusions

According to our study results, a pubertal LH value was observed in69.4% of the children who underwent priming and in 44.4% of those who did not undergo priming. These results imply no substantial effect of priming on the results of the puberty test (LHRH). Therefore, performing a growth hormone stimulation test and a puberty test (LHRH) on the same day can be considered in children who undergo priming.

232

Persistent and Profound Pan-Adrenal Steroidogenic Inhibition Long After Osilodrostat Discontinuation

Yael Sofer[1,2], Sher Matsri[1], Gabi Shefer[1], Yona Greenman[1,2], Karen Tordjman[1,2]
[1]*Tel Aviv Sourasky Medical Center, Institute of Endocrinology and Metabolism*
[2]*Grey Faculty of Medical and Health Sciences, Tel Aviv University*

Background

Osilodrostat, a potent CYP11B inhibitor, is an effective treatment for hypercortisolism in Cushing's disease (CD). Adrenal insufficiency (AI), reported in ~40% of treated patients, is usually reversible after dose reduction or discontinuation. We report a case of exceptionally prolonged AI with sustained pan-adrenal steroidogenic suppression after Osilodrostat withdrawal.

Case Description

This man presented in 2012 at age 56 with clinical features of Cushing's syndrome; CD was confirmed biochemically and by IPSS. Initial transsphenoidal surgery (TSS) resected an ACTH-positive microadenoma, resulting in transient remission. Subsequent biochemical relapse without radiological evidence of residual disease led to a second, exploratory TSS, which was unsuccessful, and despite stereotactic radiotherapy the patient remained active. Partial biochemical control was intermittently achieved between 2013 and 2022 with cabergoline and ketoconazole; cabergoline was discontinued in late 2021 due to impulse control disorder, resulting in disease exacerbation.

Osilodrostat was initiated in March 2022 and titrated to 10 mg twice daily. By August 2022, biochemical control was achieved, with morning serum cortisol in the normal range, ACTH concentrations were 7–8-fold the upper limit of normal (ULN), 11-deoxycortisol was markedly elevated (1159 nmol/L; reference 0–57), and suppressed aldosterone. During subsequent dose reduction to 5 mg twice daily, cortisol levels remained controlled while ACTH continued to rise and aldosterone remained undetectable.

In October 2023, the patient was admitted with mild hyponatremia. Morning cortisol was 35 nmol/L, ACTH approximately 20-fold the ULN, aldosterone was still suppressed, and plasma direct renin was6-fold the ULN. Osilodrostat was discontinued and glucocorticoid replacement initiated; mineralocorticoid replacement was added more recently. Over 27 months following OSI discontinuation, morning cortisol has remained subnormal (typically 100–150 nmol/L), ACTH persistently elevated (~8-fold upper limit), and adrenal steroidogenic intermediates (11-deoxycortisol, 17-hydroxyprogesterone, androstenedione, and DHEAS) consistently suppressed or at the lower end of the reference range. Under combined glucocorticoid and mineralocorticoid replacement, the patient's clinical condition has now greatly improved.

Discussion and Conclusion

Osilodrostat-induced AI is typically reversible. Since 2023, approximately 10 cases of persistent AI after Osilodrostat withdrawal have been reported, half of them in subjects with CD, with a median duration of ~11 months (IQR ~3–19). In most cases, mineralocorticoid synthesis was preserved, reflecting preferential CYP11B1 inhibition. The mechanism underlying the sustained upstream inhibition of all adrenal steroidogenic pathways observed here remains unknown. This case is unique in demonstrating 27 months of post-discontinuation AI with global suppression of glucocorticoid, mineralocorticoid, and androgen pathways, expanding the spectrum of Osilodrostat-associated adrenal impairment.

233

High and very high-risk fracture risk among patients with a non-osteoporotic range bone mineral density in a DXA database from a tertiary medical center

Yehudit Eden-Friedman[1,2], Iris Vered[1], Nimrod Tripto[3], Noga Minsky[1,2], Yael Levy-Shraga[2,4], Pnina Rotman-Pikielny[2,5], **Liana Tripto-Shkolnik**[1,2]

[1]*Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center*

[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

[3]*Recah Institute of physics, The Hebrew University of Jerusalem, Jerusalem, Israel*

[4]*Pediatric Endocrinology Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center*

[5]*Department of Endocrinology, Meir Medical Center*

Background: Fracture risk assessment has become a mainstay of osteoporosis management. Treatment paradigms for patients with a high or, especially, very high fracture risk based on FRAX assessment prioritize first-line anabolic treatment, even when bone mineral density (BMD) is in the non-osteoporotic (NOP) range. However, data regarding the prevalence of high or very high fracture risk among patients with NOP-range BMD are scarce.

Methods: We utilized computerized BMD data from a tertiary medical center between 2024 and 2025. BMD was measured by the Lunar Prodigy Advance densitometer, and country-specific FRAX calculation ± Trabecular Bone Score (TBS) adjustment was performed by the Encore v18 software. Risk factors were reported by a self-administered questionnaire. Patients were classified as osteoporotic according to T-score ≤-2.5 at either the femoral neck, total hip, or at least two lumbar spine vertebrae. High/very high fracture risk was defined as ≥3/4.5% for hip, or ≥20/30% for major osteoporotic fractures (MOF), respectively. Statistical analysis was performed using Python.

Results: Five thousand and fifteen patients aged 40 years or older (40.3% males, age 66.8 ± 8.9 years) performed BMD test during the study period and were included. Overall, 1523 (30.4%) were classified as osteoporotic and 3492 (69.6%) with a NOP BMD. Among those with a NOP BMD, 1054 (30.2%) had high hip fracture risk, while 639 (18.3%) had very high risk. In contrast, regarding MOF, only 199 (5.7%) had high risk, and 52 (1.5%) had very high risk. TBS adjustment did not significantly change these proportions (high/very high hip fracture risk: 28.9%, p=0.248/17.2% p=0.247, high/very high MOF risk 4.7%, p=0.067;/1.0%, p=0.051).

Patients with BMD-defined osteoporosis, compared to patients in the NOP high-risk group, were younger (67.9 vs. 73.8 years, p0.001), more likely to be female (82.6% vs. 55.6%, p0.001), and to have lower BMI (25.5 vs. 27.1 kg/m², p0.001). Among those with NOP-range BMD, the mean lumbar spine1-4/femoral neck/total hip T-score was 0.10±1.58/-1.24±0.86/-0.56±1.07, respectively.

Conclusions: The proportion of patients with high or very high fracture risk categories despite NOP BMD is substantial and driven primarily by hip fracture risk. These data can inform reimbursement policy decisions regarding first-line anabolic treatment.

235

Human Gastric Organoids as a Platform to Study Ghrelin Cell Differentiation and Function

Amit Elad[1], Deborah Duran[2], Michelle Malis[1], Haya Benhayon[1], Dana Orzech[1], Esther Forkosh[3], Orli Halstuk[2], Doron Kleiman[1], Ariel Benson[3], Ronit Grinbaum[4], Idit Shiff[5], Abed Nasereddin[5], Liron Birimberg-Schwartz[2], Rachel Ben-Haroush Schyr[1], Myriam Grunewald[2], Danny Ben-Zvi[1]

[1]*Department of Developmental Biology and Cancer Research, The Hebrew University of Jerusalem*

[2]*Organoid Center, Hadassah University Medical Center*

[3]*Institute of Gastroenterology and Liver Disease, Hadassah University Medical Center*

[4]*Department of Surgery, Hadassah-Hebrew University Medical Center*

[5]*Genomics Applications Laboratory, Core Research Facility, The Hebrew University of Jerusalem*

Corpus Endocrine cells (CECs) of the stomach include mainly ghrelin-secreting X-cells which regulate appetite, gastric motility, growth hormone secretion and neural function, and histamine-secreting cells, which control gastric acid secretion. These hormones and their receptors are drugs-targets for a wide range of medical disorders. Despite their significance, basic mechanisms that underlie the basic biology of the cells and regulate their function in humans are largely unknown, due to species-specific differences in gastric biology, and lack of validated in-vitro systems.

Analysis of single-cell-mRNA-seq of human gastric biopsies revealed that initial differentiation of CECs involves the expression of the transcription-factor ASCL1 without expression of NGN3, the main factor in differentiation of all endocrine cells in the intestines. ASCL1 is critical in the development of pulmonary endocrine cells (PNECs) and specification of serotonin-secreting enterochromaffin-cells in the intestine.

We overexpressed ASCL1 using AAV and lentiviral infections in human organoids and murine stomachs in-vivo, to test if ASCL1 is sufficient to generate CECs. Histological analyses show a profound induction of endocrine cells including X-cells following ASCL1-overexpression. Single-cell analysis corroborated this result and showed that infected cells differentiate into X-cells, serotonin-secreting cells and PNEC-like cells, demonstrating the potential plasticity of endocrine cells.

Establishing gastric organoids as a model system to study the biology of human CECs will allow us to understand the basic cell biology of ghrelin secretion and opens exciting possibilities to affect obesity, cachexia, body composition, mood disorders, sleep and a range of physiological and pathophysiological processes regulated by ghrelin.

236

Higher panomen-3 grade predicts the need for additional interventions following surgery in patients with non-functioning pituitary macroadenomas

Efrat Markus[1,2], Yaron Rudman[2,3], Genady Drozdinsky[2,4], Ilan Shimon[2,3], Shlomit Koren[1,2]
[1]*Endocrine and Diabetes Institute, Shamir Medical Center*
[2]*Gray Faculty of Medical & Health Sciences, Tel Aviv University*
[3]*Institute of Endocrinology, Beilinson Hospital, Rabin Medical Center*
[4]*Infectious Diseases Unit, Beilinson Hospital, Rabin Medical Center*

Introduction: In 2024, the Pituitary Society proposed the Pituitary Adenoma Nomenclature 3 (PANOMEN-3) classification for assessing the prognosis of pituitary tumors. The rationale behind this new classification was to enable the prognostic assessment of tumors managed surgically and conservatively – a feature particularly relevant for patients with non-functioning pituitary adenomas (NFPAs), which are increasingly managed non-surgically.

Aim: To assess how PANOMEN-3 grade, both at diagnosis and postoperatively, relates to the likelihood and timing of additional treatment, and its potential utility in guiding intervention decisions in patients with non-functioning pituitary macroadenomas (macro-NFPAs).

Methods: This is a retrospective cohort study. We conducted a computerized search in Rabin and Shamir medical centers databases for the diagnosis of macro-NFPAs recorded between the years 1974-2024. Of 210 patients, 180 had at least one year of pituitary MRI follow-up and were included in the analysis. Clinical, biochemical, and imaging data were collected to assess the PANOMEN-3 grade at diagnosis and postoperatively.

Results: Our cohort included 180 patients (80 females, 44.4%; age at diagnosis, 61.0±14.1 years), of whom 116 underwent transsphenoidal surgery (TSS). Median follow-up was 5 years [IQR 2–10]. After initial TSS, the proportion of patients requiring additional treatment (including repeat TSS and/or dopamine agonist therapy and/or radiotherapy) increased with higher PANOMEN-3 grade at diagnosis (Grade 1: 25.6%, Grade 2: 35.6%, Grade 3: 50%, p=0.093) and postoperatively (Grade 0: 0%, Grade 1: 28.3%, Grade 2: 46.5%, Grade 3: 75%, p0.01). Median time from first TSS to additional treatment was shorter with increasing PANOMEN-3 grade. This trend was observed both at diagnosis (Grade 1: 54 months [IQR 16–88], Grade 2: 47 months [IQR 12–97], Grade 3: 5 months [IQR 3–24], p=0.041) and postoperatively (Grade 1: 68 months [IQR 16–94], Grade 2: 24 months [IQR 12–53], Grade 3: 5 months [IQR 3–16], p=0.079).

Conclusions: Our data indicate that higher PANOMEN-3 grade, both at diagnosis and postoperatively, was associated with an increased likelihood of requiring additional treatment after surgery and earlier. This highlights the potential of PANOMEN-3 grade to guide decisions regarding the intensity of intervention at diagnosis, and to predict the need for additional treatment in patients with macro-NFPA.

237

High early mortality in subclinical hypothyroidism previously unrecognized

David Strrich[1], Ariel israel[2], Rona Lugan[3], Shalom Edri[4], David Gillis[5]
[1]*Pediatric Specialists Clinic, Endocrinology and Diabetes, Clalit Health services, and Pediatric endocrinology unit, Shaare Zedek Medical Center*
[2]*Leumit Research Institute, Leumit Health Services, School of Public Health, Gray Faculty of Medical & Health Sciences, Tel Aviv University*
[3]*The Eisenberg R&D Authority, Shaare Zedek Medical Center*
[4]*Health Information Center, Clalit Health Services, Jerusalem, Israel*
[5]*Department of Pediatrics and Pediatric Endocrinology Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*

Context: Subclinical hypothyroidism, a state of high serum TSH with normal free thyroxine (FT4) levels, has been associated with mortality but the time of highest risk is unknown.

Objective: To test the correlation between subclinical hypothyroidism and increased mortality and its timing.

Design & Setting: The study was based on a Clalit Health Services cohort reported previously. In Clalit, the electronic medical records contain demographic data, laboratory test results, medications prescribed, and coded diagnoses from patient encounters. The cohort included 2,453,091 thyroid function tests drawn from 365,965 distinct patients, of whom 276,649 were aged between 18 and 95. We excluded patients after thyroid surgery, or drugs affecting thyroid hormone levels at any time. FT4 test results were converted to Age and Gender Adjusted Percentiles (AGAPs). The hazard ratio for death was tested for normal TSH, defined as up to 4.77 mIU/l, borderline as 4.78-9.99 mIU/l and subclinical hypothyroidism (10 mIU/l or above). Normal FT4 AGAPs were defined as between the 3rd and 97th percentiles. Normal absolute FT4 levels were defined as above 12 pmol/l.

Participants: Only sets of thyroid function tests including at least results for TSH and FT4 were included. There were a total of 42038 sets of tests with 33704, 8067 and 267 classified as normal, borderline and subclinical respectively when using FT4 AGAPs as the standard. The cohort sizes differed when using absolute FT4 values as standard.

Main outcome measure: Hazard ratio for death.

Results: In the first three months after the test mortality in the subclinical group was 28 fold that of the normal group when using FT4 AGAP as the standard and 17 fold when using absolute values. Mortality gradually declined and by 5 years was equal in all groups.

Conclusion: Subclinical hypothyroidism should be seen as a warning sign for early mortality.

238

Three-Dimensional Characterization of Neural–Endocrine Arrangement during Embryonic Development of the Pancreas.

Saada Naim[1], Anna Parnis[1], Nimrod Rotem[1], Nadav Sharon[1]
Faculty of Biology, Technion

Type I diabetes is an autoimmune disease that destroys insulin-producing beta cells in the pancreatic islets of Langerhans. Cadaveric islet transplantation can treat type I diabetes but is limited by donor scarcity. Generating beta cells from human embryonic stem cells (hESCs) offers a potentially unlimited source; however, current differentiation protocols remain inefficient, underscoring the need to better understand natural islet development.

Islet architecture arises through the temporal differentiation of pancreatic progenitors: early progenitors generate alpha cells that form the mantle, whereas later progenitors produce beta cells that occupy the core. The correlation between cell identity and position suggests that interactions with non-endocrine cells influence endocrine fate. Notably, several reports point to involvement of neuronal factors in shaping islet architecture.

To map neuronal–islet spatial relationships during pancreatic development we employed expansion microscopy, a novel imaging technique enabling nanoscale imaging of biological specimens using conventional microscopy platforms. This approach enabled high-resolution imaging of islet–neuron interactions across key developmental stages.

Our preliminary results show that the neuronal system infiltrates the pancreatic region concurrently with endocrine cells emergence, emphasizing its role in early endocrine processes. By E15.5—when endocrinogenesis peaks—we identified a distinctive neuronal arrangement in which neurons form a “neuronal cage” surrounding the endocrine cells. This structure becomes more prominent as development advances. Uncovering its role is expected to clarify how neuronal signaling orchestrates islet morphogenesis, with implications for improving beta cell differentiation protocols and advancing regenerative therapies for diabetes.

239

Vitamin A Deficiency and Retinopathy on Long-Term Somatostatin Analogue Therapy: Case Presentation and Literature Review.

Esther Osher[1], Ido Wolf[2], Ravit Geva[2], Dan Mirelman[2], Yael Sofer[1], Limor Ben-Haim[1], Yona Greenman[1]

[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center. Gray Faculty of Medical and Health Sciences, Tel-Aviv University*

[2]*Department of Oncology, Gray Faculty of Medical and Health Sciences, Tel-Aviv University.*

An 86-year-old female presented with mesenteric neuroendocrine tumor (NET) Grade 1 (Ki67 1%), in May 2021. Due to disease progression, patient underwent palliative small bowel resection, and treated with somatostatin analog therapy, Sandostatin LAR 30mg administered monthly, since September 2021.

Current Issue: On November 2023, visual symptoms, full-field electroretinogram revealed retinal dysfunction affecting both rod and cone photoreceptors, with confirmed vitamin A deficiency (0.02µg/ml). Symptoms improved 4 days following vitamin A supplementation.

Vitamin A deficiency retinopathy is a vision-threatening condition that, while uncommon in developed countries, typically results from malabsorption due to bowel surgery or medication effects rather than poor nutrition. Data on the link between vitamin A deficiency in patients with NETs or endocrine disorders, treated with somatostatin analog is rare.

Literature review of 55 patients (19 acromegaly, 36 NETs) receiving long-term somatostatin analogue treatment18 months showed vitamin A deficiency in 6%, causing night blindness in 3 NET patients. Risk factors included extended bowel resection and older age. Additionally, other fat-soluble vitamin deficiencies were common (K1: 63%, E: 58%, D: 28%), with 78% having at least one deficiency, 32% showing multiple deficiencies.

Conclusions: Fat-soluble vitamin deficiencies are significantly more common than previously thought in long-term somatostatin analogue users including Vitamin A. Regular monitoring and supplementation are recommended, particularly for patients with intestinal resection.

240

Neurochemical Receptor Expression in Ovarian Cells: A Cross-Species Analysis of Neural-Ovarian Communication Pathways

Mika Colin Trabelsi[1], Anat Kahan[1]
Department of Animal Sciences, The Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem

Reproductive function is classically regulated by the hypothalamus-pituitary-gonadal (HPG) axis, where gonadotropin-releasing hormone (GnRH) neurons drive pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. These gonadotropins regulate follicle growth, ovulation, and steroid hormone production that unfolds over hours to days. However, the ovary also receives direct peripheral nervous system (PNS) innervation forming the ovarian PNS (oPNS). Despite functional evidence that oPNS regulates follicular development and steroidogenesis, the molecular landscape of neural-ovarian communication remains incompletely characterized.

To address this gap, we systematically analyzed single-cell RNA-sequencing datasets from mouse, sheep, and human ovaries to map neurochemical receptor and axon guidance molecule expression across granulosa, theca, stromal, immune, epithelial, and endothelial cells. Highly expressed receptors were identified using statistical thresholds.

We identified that FSH and LH receptors showed expected expression in granulosa and theca cells, validating our approach. We also identified insulin communication pathways: insulin receptors were conserved across all species in granulosa and theca/stroma cells, consistent with insulin`s role in ovulation and parasympathetic regulation. Stress-responsive receptors showed strong conservation: adrenomedullin (sympatho-inhibitory) in endothelial/epithelial cells across all species; glucocorticoid/mineralocorticoid receptors in human and mouse across multiple cell types, linked to stress-mediated follicle maturation and polycystic ovarian syndrome (PCOS).

Axon guidance molecules showed extensive conservation across species. Robo receptors (ROBO1, ROBO2, ROBO4) were expressed in granulosa, theca/stroma, and endothelial cells across all three species, regulating follicle atresia through granulosa cell apoptosis. Semaphorin family members (SEMA3C, SEMA7A) were conserved in granulosa and stromal cells; SEMA7A regulates follicle architecture and is downregulated at ovulation to enable tissue remodeling. SLIT2 expression in endothelial and stromal cells suggests active guidance of nerve fibers to specific ovarian compartments. These findings reveal that axon guidance pathways, traditionally associated with neural development, are co-opted in the adult ovary to regulate follicular dynamics and maintain ovarian innervation patterns.

242

Metabolic determinants of the diabetogenic interferon response in pancreatic beta-cells

Maya Israeli[1], Shani Peleg[1], Udi Ehud Knebel[1], Chunhua Dai[2], Roni Cohen-Fultheim[3], Benjamin Glaser[1], Erez Y. Levanon[3], Alvin C. Powers[4], Agnes Klochendler[1], Yuval Dor[1]

[1]*The Hebrew University of Jerusalem, Israel*

[2]*Vanderbilt University, Nashville, USA*

[3]*Bar-Ilan University, Ramat Gan, Israel*

[4]*VA Tennessee Valley Healthcare, Nashville, TN*

Type I interferon (IFN-I) responses to double-stranded RNA (dsRNA) play a key role in early Type 1 diabetes (T1D) development, though a viral cause remains unproven. This raises the possibility that endogenous dsRNA, typically edited by the Adar enzyme, triggers an aberrant IFN-I response when RNA editing is deficient. Supporting this, a recent genetic study linked reduced RNA editing to autoimmune diseases, including T1D.

Our work shows that Adar inactivation in beta-cells (beta-AdarKO) activates a robust dsRNA-driven IFN-I response, replicating early T1D features such as insulitis, targeted beta-cell failure and death, eventually resulting in diabetes. Interestingly, increased glucose metabolism through calcium influx amplifies the IFN-I response, both by boosting dsRNA-triggered IFN-I production in beta-AdarKO islets and enhancing responses to exogenous IFN-I in wild-type islets (Knebel et al., 2024). While beta-cell workload has been linked to glucotoxicity, a role in modulating islet inflammation in T1D has not been demonstrated.

Here, using pharmacological tools, we further delineate the pathway underlying the effects of glucose on the IFN-I response in beta-AdarKO islets. We reveal NFAT as a potential critical transcription factor connecting beta-cell metabolic activity to pro-inflammatory responses in the absence of RNA editing.

Strikingly, the glucose potentiating effect on interferon signaling in wild-type islets is not mediated by the canonical glucose stimulated insulin secretion pathway, specifically membrane depolarization and Ca2+ influx. Instead, we report that the widely used T2D drug metformin attenuates the glucose-stimulated IFN-I response, putatively via mTOR pathway inhibition.

Understanding how beta-cell metabolism drives islet inflammation could unveil therapeutic targets to protect beta-cells from inflammatory damage. Our findings further suggest a preventive strategy for T1D in which targeting nutrient-sensing pathways, potentially with clinically established agents like metformin, blunts glucose-amplified type I interferon signaling before overt autoimmunity and β-cell loss occur.

244

Predictors of Response to Growth Hormone Treatment and Final Height in Medulloblastoma Survivors

Eve Stern[1], Michal Ben-Ami[1], Yael agarhS-yveL[1], Amos Toren[2], Gadi Abebe-Campino[2], Michal Yalon[2], Dalit Modan-Moses[1]

[1]*Pediatric Endocrinology and Diabetes Unit, Sheba Medical Center*

[2]*Division of Pediatric Hematology-Oncology, Sheba Medical Center*

Background: Abnormal growth patterns and impaired final height (FH) are well- recognized long-term complications of childhood medulloblastoma, however data regarding response to growth hormone treatment (GHT) and determinants of FH are scarce. We aim to describe growth characteristics and response to GHT in survivors of childhood medulloblastoma, and to identify factors associated with FH outcome.

Methods: A retrospective study comprising all pediatric patients treated for medulloblastoma in a tertiary care center between 1987-2023 and followed up for at least one year following diagnosis.

Results: 65/67 patients included in the final analysis (97%) exhibited growth retardation, of whom 38 (58%) were diagnosed with GH deficiency, and 26 were treated with GH. Fifteen GH-treated patients achieved FH, with a mean FH-SDS of -1.42±1.47. Only eight (53%) achieved FH within the normal range. The most important predictor of FH outcome in GH-treated patients was height-SDS at initiation of treatment.

Conclusion: Growth retardation and GH deficiency are observed in the vast majority of medulloblastoma patients. Our results suggest that early identification and treatment of GH deficiency are crucial for optimization of FH outcome. Long-term safety of GHT is still a concern and should be discussed with the family prior to initiating treatment.

245

Immune Checkpoint Inhibitor-Related Hypophysitis: Tel Aviv Sourasky Medical Center Cohort

Ruti Karov[1], Esther Osher[1,2], Yona Greenman[1,2]
[1]*Endocrinology Metabolism And Hypertension, Tel Aviv Souraski Medical Center*
[2]*Faculty Of Medicine, Tel-Aviv University*

Background:

Immune checkpoint inhibitor (ICI)-related hypophysitis is a clinically high-impact immune-related adverse event. Presentation is frequently nonspecific and may be misattributed to malignancy or cancer therapy, while ACTH deficiency can be rapidly life-threatening if unrecognized. We describe a real-world cohort from a tertiary Endo-Oncology Clinic to inform timing, imaging yield, co-occurring irAEs, and outcomes.

Methods: We retrospectively reviewed medical records of adult cancer patients evaluated in the Endo-Oncology Clinic at Tel Aviv Sourasky Medical Center with ICI-related hypophysitis (ICI initiation: 30-Dec-2018–05-May-2025; hypophysitis diagnosis: 10-May-2020–04-Jan-2026). Patients who received systemic glucocorticoids for 2 months in proximity to diagnosis were excluded.

Results: We identified 35 patients with suspected ICI-related hypophysitis; six were excluded due to systemic glucocorticoid therapy for 2 months near diagnosis, leaving 29 patients for analysis. Mean age at diagnosis was 65.8±11.8 years and 62% were female. Most patients received PD-1/PD-L1 inhibitors (82%) while 17% received PD-1+CTLA-4. Median time from ICI initiation to hypophysitis was 265 days (IQR 189–344; range 97–714) and was shorter with PD-1+CTLA-4 versus PD-1/PD-L1 (156 [152–164] vs 295 [229–366] days; p0.001). Fatigue/weakness occurred in 90% and hyponatremia in 31%. Median morning cortisol was 0.49 µg/dL (IQR 0.28–0.96) with low ACTH (median 1.50 pg/mL, IQR 1.50–2.62; n=22). Pituitary MRI was performed in 17/29 and showed abnormalities in 7/17 (41%). ACTH deficiency was isolated in most patients; central hypothyroidism occurred in 3% and gonadotropin deficiency in 10% (17% NA/not assessed). Other irAEs were recorded in 48%, most commonly thyroiditis (34%). No adrenal axis recovery was documented.

Conclusions: In our tertiary-center cohort, ICI-related hypophysitis typically developed months after ICI initiation and was dominated by persistent ACTH–cortisol deficiency, and showed earlier onset under PD-1+CTLA-4, with moderate MRI yield and frequent co-occurring irAEs. These findings support a low threshold for endocrine evaluation in symptomatic ICI-treated patients and structured long-term follow-up for adrenal insufficiency.

Table 1. Patient characteristics and clinical features of ICI-related hypophysitis (Tel Aviv Sourasky Medical Center), N=29

Values are n (%) unless otherwise specified. Continuous variables are shown as mean ± SD or median (IQR).

Characteristic	Overall
Demographics	
Age at hypophysitis diagnosis, years (mean ± SD)	65.8 ± 11.8 (n=29)
Female sex	18 (62%)
BMI, kg/m² (mean ± SD)	25.4 ± 4.8 (n=28)
Underlying malignancy	
Lung adenocarcinoma	6 (21%)
Renal cell carcinoma	5 (17%)
Colorectal cancer	5 (17%)
Melanoma	4 (14%)
Gastric cancer	3 (10%)
Squamous cell carcinoma	2 (7%)
Urothelial carcinoma (TCC)	1 (3%)
Breast cancer	1 (3%)
Hodgkin lymphoma	1 (3%)
Ovarian cancer	1 (3%)
ICI regimen	
PD-1 inhibitor	24 (83%)
PD-1 + CTLA-4 (combination)	5 (17%)
Background glucocorticoid exposure at hypophysitis diagnosis	
None	21 (72%)
Intermittent	4 (14%)
Inhaled	1 (3%)
Topical	0 (0%)
Systemic (Up to two months)	3 (10%)
Timing	
Time from ICI start to hypophysitis diagnosis, days (median, IQR)	265 (189–344) (range 97–714)
PD-1/PD-L1	295 (229–366) (n=24)
PD-1 + CTLA-4	156 (152–164) (n=5)
Presentation (not mutually exclusive)	
Fatigue/weakness	26 (90%)
Hyponatremia (presenting feature)	9 (31%)
Headache	2 (7%)
Fever	1 (3%)
Biochemistry at diagnosis	
Morning cortisol, µg/dL (median, IQR)	0.49 (0.28–0.96) (n=29)
ACTH, pg/mL (median, IQR)	1.50 (1.50–2.62) (n=22)
Sodium, mEq/L (median, IQR)	134.5 (131.8–138.0) (n=28)
Glucose, mg/dL (median, IQR)	85.5 (76.5–102.5) (n=28)
Pituitary MRI	
No pituitary abnormality	10 (34%)
Pituitary abnormality present	7 (24%)
MRI not performed / not available	12 (41%)
Additional pituitary axes	
Central hypothyroidism (TSH deficiency)	1 (3%)
Gonadotropin deficiency	No 21 (72%) • Yes 3 (10%) • NA/not assessed 5 (17%)
Prolactin elevation	No 21 (72%) • Yes 0 (0%) • NA 8 (28%)
Other immune-related adverse events (OTHER irAEs field)	
Any additional irAE	14 (48%)
Thyroiditis	10 (34%)
Encephalitis	1 (3%)
Colitis	1 (3%)
Hepatitis	1 (3%)
Aseptic meningitis	1 (3%)
Pneumonitis	1 (3%)
Outcome	
Adrenal axis recovery	Yes 0 (0%) • No 27 (93%) • N/A 2 (7%)

New-onset autoimmune endocrine disorders in people living with post-traumatic stress disorder

Yovel Cohen[1,2], Meir Schechter[1,2], Dvora Rywka Sehtman-Shachar[1,2], Ofri Mosenzon[1,2,3], Genya Aharon-Hananel[1,2], Gil Leibowitz[1,2]

[1]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center of the Hebrew University, Jerusalem, Israel.*

[2]*Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel.*

[3]*Regeneron Pharmaceuticals Inc., New York, New York, USA.*

Abstract

Background: Small observational studies suggest that post-traumatic stress disorder (PTSD) may be associated with an increased risk of autoimmune disorders, including endocrine disorders. However, most prior studies focused on male military veterans comprehensive, thus, epidemiological data remain limited. Since October 7, 2023, the incidence of PTSD is markedly increased among Israeli soldiers and civilians; therefore, studying the implications of PTSD on the development of autoimmune endocrine disorders is timely and important.

Methods: In this retrospective cohort study, we used the TriNetX global platform, which contains electronic health records of over 170 million people worldwide. We propensity-score matched (1:1) individuals with chronic PTSD versus individuals without PTSD (2005–2025). Follow-up continued for up to 5 years. Cox proportional-hazards regression models were used to assess the risk of an incident composite outcome comprising 33 autoimmune diseases. Each autoimmune disease was also analyzed as an individual outcome, including type 1 diabetes mellitus (T1D), Hashimoto's hypothyroidism, and Addison's disease. Analyses were repeated in subgroups defined by sex, age, race, and ethnicity.

Results: The matched cohort included 306,792 individuals (mean age 38.5±16.6 years; 64.1% women). Over 1,022,248 person-years, new-onset autoimmune disorders (the composite outcome of 33 autoimmune diseases) occurred in 12,845 (8.37%) individuals with PTSD and 9,988 (6.51%) individuals without PTSD (HR 1.33; 95% CI 1.30–1.37). For endocrine outcomes, the HR for T1D was 2.29 (95% CI 2.10–2.50), for Hashimoto's hypothyroidism 1.29 (95% CI 1.24–1.33), and for Addison's disease 2.64 (95% CI 2.05–3.39). In subgroup analyses, the HR for any autoimmune disorder was 1.32 (1.29–1.36) in women and 1.38 (1.35–1.41) in men. Across age groups, HRs were 1.30 (1.25–1.35) for ages 18–40, 1.34 (1.25–1.34) for ages 40–60, and 1.31 (1.26–1.36) for ages ≥60. Regarding race, HRs were 1.33 (1.30–1.37), 1.09 (1.03–1.16), and 1.24 (1.14–1.35) in those of White, African American, and Asian/other origins, respectively.

Conclusion and Relevance: PTSD is associated with increased incidence of autoimmune endocrine disorders, including type 1 diabetes, Hashimoto`s thyroiditis and Addison's disease. The risk for autoimmunity is increased across different genders, ages and ethnic groups. These findings have important implications for public health.

249

LXRs participate in the fasting response by assisting C/EBPβ binding to enhancers and promoting the fasting transcriptional program

Tali Gorbonos[1], Maria C. Romero Florian[2], **Hadar Shalev**[1], Noga Korenfeld[1], Cigdem Sahin[2], Dana Goldberg[1], Talia Radushkevitz-Frishman[1], Mariana Anosov-Babi[1], Angela Yan[2], Meital Charni-Natan[1], Meirav Bar-Shimon[1], Carolyn L. Cummins[2], Ido Goldstein[1]

[1]*The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem. Rehovot, Israel, Institute of Biochemistry, Food Science and Nutrition*

[2]*Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada*

Upon fasting, a group of transcription factors (TFs) activates an extensive transcriptional program in the liver to alter hepatocyte metabolism and cope with fasting. This is achieved by TF-mediated activation of enhancers, which become more accessible, leading to gene induction. Liver X receptors (LXRα and LXRβ, collectively termed here LXRs) are important TFs that are known to participate in transcriptional programs after feeding but their role in fasting is unclear. Here, we examined the effect of LXR deletion on the transcriptional and chromatin programs activated in the fasted and fed states. We profiled the liver's transcriptome and genome-wide chromatin accessibility in both single knockout of each LXR isoform as well as double knockout. We found that double knockout of LXRs impairs fasting-induced genes and fasting-activated enhancers. Examining the genome-wide profile of LXRα by ChIP-seq showed it directly binds and activates enhancers. Surprisingly, we found that LXRs indirectly assist the binding of CCAAT/enhancer binding protein beta (C/EBPβ) to enhancers during fasting. C/EBPβ is a key TF regulating the fasting response, and its genome-wide binding was profoundly perturbed with the lack of LXRs. The cooperation between LXRs and C/EBPβ promoted fasting-dependent gene induction. These findings unravel a hitherto unknown role for LXRs in the fasting response whereby LXRs bind and activate enhancers, assist C/EBPβ binding, and promote gene induction. This shows the complex cooperation of TFs in regulating gene expression to maintain homeostasis during fasting and places LXRs as novel regulators of the fasting response.

250

The effect of early-harvested extra virgin olive oil consumption on pregnant women at risk for preeclampsia: preliminary results of an interventional pilot study

Esti Ditchi[1,2], Efrat Monsonego Ornan[1], Simon Shenhav[2,3], Daniela Abigail Navarro[4], Avi Rimler[5], Alexander Brandis[6], Ido Solt[7], Eyal Anteby[3,8], Yaniv Ovadia[1,8]

[1]*Department of Biochemistry, Food Science and Nutrition, The Hebrew University of Jerusalem*

[2]*High Risk Pregnancy Unit, Obstetrics and Gynecology Department, Barzilai University Medical Center*

[3]*Faculty of Health Sciences, Ben-Gurion University of Negev*

[4]*Department of Nutrition Sciences, Faculty of Health Sciences, Ariel University*

[5]*Laboratory of Clinical Biochemistry, Barzilai University Medical Center*

[6]*the Targeted Metabolomics Unit, Department of Life Sciences Core Facilities, Weizmann Institute of Science*

[7]*High Risk Pregnancy Service, Rambam Health Care Campus*

[8]*Obstetrics and Gynecology Division, Barzilai University Medical Center*

Background: Preeclampsia (PE) affects 3–5% of all pregnancies and up to 30% in high-risk groups. Its pathophysiology involves placental hypoxia and oxidative stress. Extra virgin olive oil (EVOO) is rich in polyphenols and antioxidants, with early-harvested EVOO (EVOOEH) containing significantly higher concentrations of these bioactive compounds. Emerging data suggest that EVOO may mitigate placental inflammation and reduce the risk of gestational diabetes mellitus (GDM) and PE.

Objective: To evaluate the impact of EVOOEH consumption on hypertensive indices and pregnancy outcomes among women at high risk for PE.

Methods: This randomized, single-masked interventional pilot study recruited high-risk pregnant women (8–16 weeks gestation). Risk factors for inclusion included obesity (BMI 25 kg/m²), advanced maternal age, chronic hypertension, multifetal gestation, Antiphospholipid Syndrome (APLA), and glucose intolerance. Participants were assigned to either a control group receiving standard Mediterranean diet counseling (monitored via I-MEDAS) or an intervention group receiving the same counseling with addition of 42 mL/day of EVOOEH recommendation (provided by researchers). Primary outcomes include GDM and PE incidence; secondary outcomes include blood pressure (BP) and the sFlt-1/PlGF ratio.

Results: Preliminary analysis of 26 participants (n=13 per group) showed no significant baseline differences in age, BMI, or initial BP. Following a 4-week intervention, the EVOOEH group demonstrated a trend toward reduced diastolic BP (DBP) (68±10 vs. 63±8 mmHg, p=0.06), while no such change occurred in the control group (71±11 vs. 70±8 mmHg, NS). Mediterranean diet adherence scores remained stable across both groups.

Conclusion: Preliminary findings suggest that daily EVOOEH consumption can possibly support BP reduction in women at risk for PE, presumably through antioxidant-mediated decrease of microvascular damage. Further recruitment and comprehensive analyses are ongoing to confirm these effects on clinical pregnancy outcomes.

251

Real-World Multicenter Outcomes following transition to Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia and Adrenal Insufficiency

Anat Segev-Becker[1], Talia Jacobi-Polishook[2], Liat Perl[1], Larisa Nauogolny[3], Jessica Sack[4], Nitzan Dror[5], Alon Eliakim[5], Shirli Abiri[6], Tal Ben Ari[6], Rivka Dresner-Pollak[7], Yael Levy-Shraga[8], Meir Frankel[9], Neta Loewenthal[10], Michal Cohen[11], Merav Fraenkel[12], Dmitry Shklovski[13], Nir Lasman[14], Alina German[15], Yardena Tenenbaum Rakover[16], Dania Hirsch[17], Svetlana Turkot[18], Mzia Sapir[19], Liza Paley[18], Liat Sasson[17], Marianna Rachmiel[2], Miriam Steinschneider[20], David Shaki[21], Sigal Shaklai[4], Ilana Zalmon Koren[22], Naomi Weintrob[23]

[1]*The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

[2]*Pediatric Endocrinology Institute, Shamir (Assaf Harofeh) Medical Center, Beer Yaakov, Israel.*

[3]*Meuchedet Health Services, Rishon LeZion, Israel*

[4]*Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel*

[5]*Pediatric Endocrinology Unit, Meir Medical Center, Kfar-Saba, Israel.*

[6]*Pediatric Endocrinology and Diabetes Unit, Edith Wolfson Medical Center, Holon, Israel*

[7]*Department of Endocrinology, Hadassah Medical Center, Jerusalem, Israel*

[8]*Pediatric Endocrine and Diabetes Unit, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel*

[9]*Endocrinology Unit, Shaare Zedek Medical Center, Jerusalem, Israel*

[10]*Pediatric Endocrinology Unit, Ben Gurion University Medical Center, Beer Sheva, Israel*

[11]*Pediatric Endocrinology Unit, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel.*

[12]*Endocrine Unit, Soroka Medical Center, Beer-Sheva, Israel*

[13]*Endocrinology, Clalit Health Service South District*

[14]*Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel-Hashomer, Israel*

[15]*Pediatric Endocrinology and Diabetes Unit, HaEmek Medical Center, Afula, Israel*

[16]*Children's Endocrinology Consulting Center, Clalit Health Services, Afula, Israel.*

[17]*Institute of Endocrinology, Rabin Medical Center - Beilinson Hospital, Petach Tikva, Israel.*

[18]*Barzilai medical center*

[19]*Clalit Migdal Hamea, Tel Aviv*

[20]*Endocrine and diabetes institute, Shamir (Assaf Harofeh) Medical Center, Beer Yaakov, Israel*

[21]*Pediatric Endocrinology Unit, Soroka University Medical Center, Beer Sheva, Israel*

[22]*Pediatric Endocrinology Unit, Lady Davis Carmel Medical Center and Clalit Health Services, Haifa, Israel*

[23]*Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel*

Background: Both congenital adrenal hyperplasia (CAH) and adrenal insufficiency (AI) due to other etiologies are associated with increased cardiometabolic morbidity, impaired quality of life, and increased mortality. These adverse outcomes are thought to be related, at least in part, to the inability of standard glucocorticoid (GC) replacement therapy to replicate the circadian rhythm of physiological cortisol secretion, as well as to the supraphysiological GC doses often required to suppress androgen excess in CAH. Recently, modified-release hydrocortisone (MR-HC) formulation designed to mimic circadian cortisol secretion have been shown to allow GC dose reduction in CAH and to improve fatigue and quality of life in patients with AI. However, real-world data outside controlled research settings remain limited.

Aims: To evaluate changes in glucocorticoid dosing, androgen levels, and anthropometric parameters in patients with CAH and other forms of AI following transition to MR-HC therapy.

Methods: A retrospective, multicenter chart review conducted between October 2023 and January 2026. Data are presented as median [IQR].

Results: The study population comprised 89 subjects (51 females), including 21 with salt-wasting, 14 with simple virilizing and 40 with non-classic CAH, 6 with 11β-hydroxylase deficiency, and 8 with adrenal insufficiency due to other causes. Age at diagnosis was 3.0 years [0.1–8.3], and age at transition to MR-HC was 19.0 years [13.8–31.0]. Hydrocortisone (HC) equivalent dose adjusted for body surface area (mg/m²) decreased significantly following transition to MR-HC, from 12.2 [9.1–15.4] to 11.0 [8.5–13.6] ($p = 0.025$). Friedman test analysis across multiple time points demonstrated a progressive reduction in HC dose after transition (p 0.001). The degree of dose reduction did not differ between patients with classic and non-classic CAH. Median androstenedione and testosterone concentrations (nmol/L) decreased from 9.0 [5.1–14.5] to 5.9 [1.7–9.1] and from 1.10 [0.60–1.58] to 0.65 [0.40–1.10], respectively (p 0.001 and $p = 0.014$). Patients with non-CAH adrenal insufficiency reported significant improvements in energy and well-being. Eleven subjects discontinued MR-HC primarily due to cost.

Conclusions: In this real-world, multicenter cohort, transition to MR-HC was associated with concomitant reductions in glucocorticoid dosing and improved androgen control. These findings support MR-HC as an effective, physiologically aligned therapeutic option for patients with congenital adrenal hyperplasia and adrenal insufficiency.

252

Real-World Comparison of the Upcoming ATA 2026 Sonographic Classification with ATA 2015 and ACR TI-RADS in Thyroid Nodules

Gali Avior[1], **Einav Gal Levin**[1], Pinchas Klein[2]
[1]*Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel., Department of Otolaryngology - Head and Neck Surgery, Sheba Medical Center, Technion University, Tel-Aviv, Israel.*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel., Division of Endocrinology, Diabetes, and Metabolism, Sheba Medical Center, Ramat Gan, Israel.*

Introduction: Ultrasound-based classifications including the American Thyroid Association (ATA) classifications and the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) are used to evaluate the risk of malignancy in thyroid nodules. However, their relative diagnostic performance and consistency across real-world cohorts remains debated. This study aimed to compare the performance of the upcoming ATA 2026 (uATA 2026), the ATA 2015 and ACR TI-RADS, and to assess agreement between observed and published risks of malignancy.

Methods: We retrospectively analyzed all biopsied thyroid nodules at a tertiary medical center between 2023 and 2025. Demographic, imaging and pathological data were collected. Each nodule was classified according to ATA 2015, uATA 2026 and ACR TI-RADS classifications. Predictive performance was evaluated using logistic regression and ROC curve analysis, with AUCs compared using DeLong's test. Calibration was assessed using the Brier score.

Results: The cohort included 304 patients with 29.3% male and mean age of 55.8 (±16.4) years. Malignancies were identified in 60 nodules (19.7%).
Discriminatory performance was similar across systems, with AUCs (95% CI) of 0.794 (0.736–0.852) for ATA 2015, 0.763 (0.696–0.829) for uATA 2026 and 0.793 (0.734–0.852) for ACR TI-RADS (all pairwise p0.195). Calibration was comparable across models, with Brier scores of 0.118, 0.124 and 0.120, respectively. Calibration plots demonstrated similar patterns of underestimation of malignancy risk in the intermediate risk range of 20–50% (or 30–50% for uATA 2026).
For predicted risk of 0-3%, all scores had matching observed risk of zero. For a predicted risk of 5%-20% (ATA 2015 low- and intermediate- risk categories, uATA 2026 low-risk category, TIRADS category 4), observed malignancy rates were 12.4%, 9.23% and 11.8%, respectively. uATA 2026 was able to predict malignancy risk for the newly refined intermediate risk, with predicted risk range of 20-50% and observed risk of 29.4%. ATA 2015 high-risk category overestimated malignancy risk (predicted risk 70%-90% vs 65.9% observed risk), whereas uATA 2026 high-risk category (predicted risk 50%) matched with observed risk of 66.7%. TIRADS category 5 (predicted risk 20%) had an observed risk of 60.4%.

Conclusions: ATA 2015, uATA 2026 and ACR TI-RADS showed good discriminatory performance, with uATA 2026 classification demonstrating a modest advantage in the intermediate risk range (20-50%). The close agreement between predicted and observed malignancy risks reflects the high quality of sonographic risk stratification in a tertiary care setting.

253

Proximal Gastric Endocrine Cells are Long-Lived and Follow a Unique Developmental Trajectory

Amit Elad[1], **Michelle Malis**[1], Yifaa Friedman[1], Rachel Ben-Haroush Schyr[1], Danny Ben-Zvi[1,2]

[1]*Developmental Biology and Cancer Research, Hebrew University of Jerusalem*
[2]*Center for Computational Medicine, Hebrew University of Jerusalem*

Gastric corpus endocrine cells consist mainly of histamine-secreting enterochromaffin-like cells (ECLs) which regulate acid secretion, and ghrelin-secreting X cells affecting gastric motility, growth hormone secretion and appetite. We recently identified that the transcription factor PTF1A, its obligate cofactors and downstream targets are expressed in gastric endocrine progenitors and mature cells in the human gastric corpus. PTF1A is required for the development of the pancreas and cerebellum, and maintains pancreatic exocrine identity in the adult. We hypothesized that PTF1A has an important role in the development and homeostasis of gastric endocrine cells.

Using histological assays in adult ptf1a-CreER mice, we confirmed PTF1A is expressed specifically in endocrine progenitors and ECLs in the mouse gastric corpus. Surprisingly, PTF1A knockout mice developed all corpus endocrine cells, demonstrating that PTF1A is not required for their differentiation. Conditional PTF1A knockout in adult mice reveals that PTF1A expression is not required for maintenance of the ECL fate, and confirmed it is required for the maintenance of pancreatic acinar cells. Pulse-chase lineage-tracing of PTF1A expressing cells showed that ECLs and X cells are exceptionally long-lived, persisting for approximately one year, contrary to the short-lived enteroendocrine cells in the intestine.

In conclusion, PTF1A is surprisingly not required for the development and maintenance of gastric endocrine cells. Its function in these cells remains to be determined. We found that gastric corpus endocrine cells are very long-lived, with potential implications to gastric carcinoid tumor biology, and to the persistence of metabolic memory following weight gain and weight loss.

254

Does the difference between Bethesda V and VI predict long term outcomes of thyroid cancer?

Marina Ioffe[1], Anna Anna Hochner-Ger[2], Ignat Schwartz[2], Reut Halperin[3], Galit Avior[4], Pinchas Klein[1,5]

[1]*Division of Endocrinology, Diabetes and Metabolism, The Chaim Sheba Medical Center, Tel Hashomer, Israel*

[2]*Institute of Pathology, The Chaim Sheba Medical Center, Tel Hashomer, Israel*

[3]*1ENTIRE - Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Diabetes and Metabolism, The Chaim Sheba Medical Center, Tel Hashomer, Israel*

[4]*Otolaryngology Head& Neck Surgery Department, The Chaim Sheba Medical Center, Tel Hashomer, Israel*

[5]*Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

Background

Limited data exist regarding the correlation between cytologic classification and long-term clinical outcomes in thyroid cancer.

In this study we focused on patients classified as high risk for malignancy (Bethesda V and VI) to evaluate the prognostic significance of initial cytologycal classification in the long-term clinical course.

Study Aims

To compare Bethesda V and VI in terms of clinicopathologic features, treatment strategies, and long-term oncologic outcomes.

Methods

We conducted a retrospective study of patients with thyroid nodules classified as Bethesda V or VI on fine-needle aspiration (FNA), using medical records from Sheba Medical Center. Patients without available follow-up data and those managed with active surveillance were excluded. Bethesda V and IV groups were compared across clinical characteristics, treatments and response using chi-square test, Fisher's exact test and Wilcoxon rank-sum test.

Results

From 2012-2024, 5,000 FNAs were performed, of which 150 patients were classified as Bethesda V and 253 as Bethesda VI. The risk of malignancy was 93.2% for Bethesda V and 98% for Bethesda VI. A total of 298 patients with follicular cell-derived thyroid carcinoma were included in the final analysis, of which 112 were classified as Bethesda V and 186 as Bethesda VI. Classic papillary thyroid carcinoma (PTC) was the predominant histology (74%), occurring more frequently in Bethesda VI (79% vs. 66%); while aggressive PTC variants were more prevalent in Bethesda V (13% vs. 6.0%), though distribution did not differ significantly. High-grade thyroid carcinomas were rare with similar prevalence in both groups. Tumor size, extrathyroidal extension, lymphovascular invasion, lymph node involvement, and distant metastases were comparable between groups. Tracheal or esophageal invasion was more frequent in Bethesda VI (3.8% vs. 0%, $p = 0.048$). After a median follow-up of 36 months, the majority of patients achieved an excellent response to therapy (76%), with no significant difference between groups. The extent of surgery and use of radioactive iodine therapy were comparable; however, patients in the Bethesda V group more frequently required multiple surgical procedures (19% vs. 9.1%, $p = 0.016$).

Conclusions: Patients with Bethesda V and VI cytology demonstrate a very high risk of malignancy and show comparable tumor characteristics, treatment strategies, and long-term oncologic outcomes. Despite minor differences in histologic subtypes and surgical course, overall response-to-therapy rates were comparable. These findings suggest that the distinction between Bethesda V and VI has limited prognostic value for long-term outcomes, and surgical extent decisions should be similar for both categories.

256

Pregnancy Outcomes by Thyroid Autoantibody Status in Euthyroid and Subclinical Hypothyroid Women- Insights from a Nationwide Cohort study

Maya Maimon Solomon[1], Uri Yoel[2], Yuval Elhayani[3], Nitzan Burrack[3], Merav Fraenkel[2], Tamar Eshkoli[1]

[1]*DEPARTMENT OF GYNECOLOGY, SOROKA MEDICAL CENTER*
[2]*DEPARTMENT OF ENDOCRINOLOGY, SOROKA MEDICAL CENTER*
[3]*CLINICAL RESEARCH CENTER, BEN GURION UNIVERSI*

Background

Although an increased risk of miscarriage has been well documented in women with subclinical hypothyroidism and thyroid autoantibodies, the independent effect of thyroid autoimmunity on other obstetric outcomes, particularly among euthyroid and subclinical hypothyroid women, remains unclear.

Objective

To evaluate pregnancy outcomes and complications, excluding miscarriage, according to thyroid autoantibody status among euthyroid and subclinical hypothyroid women.

Methods

All live-birth pregnancies (2013–2022) among Clalit Health Services-insured women were screened. Pregnancies in women aged ≥18 years with available thyrotropin (TSH) and thyroid autoantibody (anti–thyroid peroxidase and/or anti–thyroglobulin) measurements were included; women with a history of hypothyroidism or levothyroxine treatment were excluded. Pregnancies were stratified by thyroid function and autoantibody status into euthyroid (mean pregnancy TSH 4 mIU/L) or subclinical hypothyroid (TSH ≥4 mIU/L), with or without thyroid autoantibodies (one or both). To address confounding, antibody-positive and antibody-negative groups were balanced using inverse probability weighting (IPW) based on propensity scores estimated from maternal age, ethnicity, socioeconomic status, use of in vitro fertilization, history of recurrent pregnancy loss, and smoking. Analyses included univariate comparisons of obstetric outcomes and weighted quasi-Poisson regression to estimate adjusted incidence rate ratios for composite pregnancy complications.

Results

Of 338,352 screened live-birth pregnancies, 25,484 were included in the final analysis. In univariate analyses, most maternal and neonatal outcomes were clinically comparable across groups. Although statistically significant differences were observed for selected outcomes such as gestational diabetes, labor induction, assisted delivery, premature rupture of membranes, and certain placental or amniotic fluid abnormalities, these differences were inconsistent across comparisons and did not reflect clinically meaningful increases in severe outcomes. In weighted Poisson regression analyses, thyroid antibody positivity among euthyroid women was associated with a slightly lower rate of composite pregnancy complications compared with antibody-negative euthyroid women (IRR 0.92, 95% CI 0.89–0.96). No association between thyroid antibody status and composite complications was observed among women with subclinical hypothyroidism (IRR 1.01, 95% CI 0.91–1.12). Importantly, no significant difference was identified between euthyroid antibody-negative women and subclinical hypothyroid antibody-positive women (IRR 0.96, 95% CI 0.91–1.01).

Conclusions:

Thyroid antibody positivity was not associated with clinically meaningful increases in pregnancy complications among euthyroid or subclinical hypothyroid women. These findings suggest that, in the absence of overt hypothyroidism, thyroid autoimmunity alone may not warrant intensified obstetric monitoring.

257

The impact of severe overt primary hypothyroidism on outcomes of hospitalized patients with bacteremia

Dor Eldar[1], Naftali Gross[2], Meir Frankel[1], Eli Ben-Chetrit[3], Gabriel munter[1]
[1]*Endocrinology, Diabetes & Metabolism Unit, Shaare Zedek Medical Center, Hebrew University School of Medicine*
[2]*Internal medicine Division, Shaare Zedek Medical Center, Hebrew University School of Medicine*
[3]*Infectious Diseases Unit, Shaare Zedek Medical Center, Hebrew University School of Medicine*

Background: Thyroid dysfunction is common among hospitalized patients and may adversely influence clinical outcomes in patients with bacteremia. This study evaluated whether severe overt primary hypothyroidism at admission is associated with worse outcomes among inpatients with blood culture proven bacteremia.

Methods: A retrospective cohort study was conducted at Shaare Zedek Medical Center (Jerusalem, Israel) between the years 2000 and 2024. Adult inpatients (≥18 years) with hypothyroidism, blood culture–proven bacteremia, and available thyroid function tests at admission were included. At our center, TSH is routinely measured for all hospitalized patients on admission. Hypothyroidism was defined by documented diagnosis, chronic levothyroxine use, or TSH 20 mU/L. Uncontrolled hypothyroidism was defined as TSH 10 mU/L. Outcomes included, among others, in hospital mortality and length of stay (LOS)

Results: Among 1,756 patients (mean age 82.4 ± 11.8 years; 72.4% female), in hospital mortality increased with higher TSH levels: 14% for TSH 0.35-5 mU/L, 19.3% for TSH 5–10 mU/L, 22.9% for TSH 10–20 mU/L, and 32.7% for TSH 20 mU/L. Adjusted Cox regression showed that TSH 20 was independently associated with higher mortality (HR 1.89, 95% CI 1.28–2.79, p = 0.001). A continuous TSH model confirmed incremental risk (HR 1.02 per TSH unit, p 0.001). Additional independent correlates of mortality included older age (HR 1.05, p 0.001), low albumin (HR 0.54, p 0.001), female sex (HR 1.35, p = 0.037), and vasopressor use (HR 1.77, p 0.001). Median LOS also increased with higher TSH: 8.0 days (IQR 5.0-16.0) for TSH 0.35-5 mU/L, 8.5 days (IQR 6.0-17.0) for TSH 5-10 mU/L, 11.0 days (IQR 6.0-26.0) for TSH 10-20 mU/L, and 13.0 days (IQR 7.0-21.25) for TSH 20 mU/L.

Conclusions: severe overt primary hypothyroidism, particularly TSH 20 mU/L, independently predicts higher short term mortality and is associated with prolonged hospitalization among inpatients with bacteremia. These findings support considering thyroid status as a prognostic marker in this high-risk population and warrant prospective evaluation of targeted management strategies.

258

Unusual Neuropsychiatric Presentation of Insulinoma in Two Elderly Patients Successfully Treated with EUS-Guided Radiofrequency Ablation

mikhails salman[1], Tal Schiller[1], Maysara Najjar[1], Dana Herzberg[1], Orit Twito[1]
Institute of Endocrinology, Diabetes and Metabolic Disease, Wolfson Medical Center, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel1

Background

Insulinoma is a rare cause of endogenous hyper-insulinemic hypoglycaemia with variable clinical presentation. In elderly patients, symptoms may be atypical and dominated by neuroglycopenic or neuropsychiatric manifestations, with reduced adrenergic warning signs, often leading to delayed diagnosis.

Design and methods

A retrospective report of two octogenarians with insulinoma who were diagnosed and treated in a tertiary medical center, both successfully treated with endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA).

Results

The first case involved an 88-year-old woman with multiple comorbidities who developed progressive personality changes, nocturnal agitation, and aggression without adrenergic symptoms. She was initially misdiagnosed with a primary psychiatric disorder. During an acute episode, she was found to have severe hypoglycaemia (22 mg/dL), with rapid symptom resolution following intravenous dextrose. Laboratory evaluation demonstrated elevated insulin and C-peptide levels during fasting hypoglycaemia, and imaging revealed a 14-mm pancreatic neck lesion consistent with insulinoma. EUS-RFA resulted in complete clinical and biochemical resolution, with no recurrence at 4-month follow-up.

The second case involved an 89-year-old woman with diabetes mellitus not receiving antidiabetic therapy, Parkinson’s disease, and functional decline, who presented with recurrent hypoglycaemia (30–45 mg/dL) manifesting as weakness, confusion, and falls, without adrenergic symptoms. Biochemical testing confirmed endogenous hyper-insulinemic hypoglycaemia, and computed tomography demonstrated a 10-mm hyper-vascular lesion in the pancreatic head. She underwent successful EUS-RFA with normalization of glucose levels and no recurrent hypoglycaemia at 6-month follow-up.

Conclusion

These cases highlight that insulinoma in elderly patients can mimic neuropsychiatric or neurodegenerative disorders and emphasize the safety and efficacy of EUS-guided RFA as a minimally invasive curative approach for frail or high-risk individuals

259

Intense physical exercise induces acute hyperglycemia and hyperinsulinemia in fasting, healthy adults

Doron Kleiman[1], Rachel Schyr[1], Danny Ben-Zvi[1]
Institute for Medical Research, Israel-Canada, Hebrew University of Jerusalem

Acute high-intensity physical exercise induces rapid and profound changes in glucose metabolism, yet the short-term dynamics of glucose, insulin and other hormones, and metabolites in humans are mostly uncharacterized. This study investigated the immediate metabolic effects of high-intensity exercise inducing maximal oxygen consumption (VO_2max) in healthy individuals. Participants completed a graded cardiopulmonary exercise test (CPET) lasting approximately 12 minutes, during which treadmill speed and incline were progressively increased until VO_2max was achieved. Plasma was collected 1 minute after completing the test, and at 5 and 15 minute intervals for 90 minutes.

Preliminary data from 12 subject show that plasma glucose sharply increased between 1 and 5 minutes after completing CPET by an average of 50mg/dL. Higher VO_2max, an indicator of cardiovascular fitness, was associated with a higher increase in glucose, with very fit individuals reaching levels of 190mg/dL. Insulin levels sharply increased by 6-fold within these 4 minutes to 80pM, similar to maximal post-prandial levels. Strikingly, insulin secretion rate 5 minutes after completing CPET, measured using C-peptide deconvolution, was 2-fold higher than maximal post-prandial levels reported in healthy individuals, and even those treated with semaglutide. Elevated levels of glucose and insulin persisted up to an hour after completing CPET.

Other hormones and metabolites were also affected by CPET. Mean lactate levels exceeded 11mM and declined slowly to reach baseline levels at 90min. Cortisol levels peaked 30 minutes after exercise, while testosterone and ghrelin were not affected

Collectively, these findings advance our understanding of acute metabolic and hormonal adaptations to high-intensity exercise and highlight the importance of recovery-phase regulation. Specifically, they raise fundamental questions on the regulation of plasma glucose and insulin after exercise, while the metabo-endocirne context is very different from the well-studied fasting and post-prandial states. We plan to extend the study and measure the plasma metabolome and levels of other hormones, including myokines, adrenaline and incretins to study the metabolic and hormonal response to acute exercise, and how it is related to VO_2max.

260

Metformin and risk of cancer in patients with diabetes mellitus - a large-scale population cohort

Idit Dotan[1,2], Shiri Kushnir[3], Tzippy Shochat[4], Talia Diker Cohen[1,2]
[1]*Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Institute of Endocrinology, Diabetes and Metabolism*
[2]*Tel Aviv University, Tel Aviv, Israel, Gray Faculty of Medical and Health Sciences*
[3]*Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Research Authority*
[4]*Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Statistical Consulting Unit*

Background:
Type 2 diabetes mellitus (T2DM) is associated with increased cancer risk. Observational data on the relationship between metformin use and cancer incidence are conflicting, particularly in newly diagnosed patients.

Methods:
We performed a retrospective cohort study using de-identified electronic health records from a large Israeli health maintenance organization. Adults with newly diagnosed T2DM (2005-2020) and no prior cancer were included. A landmark design was applied, defining metformin exposure during the first 3 years after diabetes diagnosis. Metformin users (≥3 prescriptions) were propensity score–matched 1:1 to non-users based on demographic characteristics, comorbidities, lifestyle factors, and concomitant medications. Incident cancer was identified using ICD-10 codes. Hazard ratios (HRs) were estimated using Cox proportional hazards models.

Results:
The matched cohort included 46,012 patients (23,006 metformin users and 23,006 non-users). Median follow-up was 6.8 years and 5.0 years, respectively. Metformin use was associated with a lower risk of incident cancer (HR 0.95, 95% CI 0.91-0.99; p=0.011). Site-specific analyses demonstrated reduced risks of urinary tract cancer (HR 0.87, 95% CI 0.79-0.96) and respiratory cancer (HR 0.91, 95% CI 0.82-1.00). No significant associations were observed for breast, digestive, or genital malignancies. Metformin users had higher HbA1c levels during follow-up but greater healthcare utilization.

Conclusion:
In a large real-world cohort of patients with newly diagnosed T2DM, metformin use was associated with a modest reduction in overall cancer incidence, driven mainly by urinary tract and respiratory cancers. These findings support a potential cancer-protective association of metformin independent of glycaemic control.

261

The role of 5-hydroxymethylcytosine and TET enzymes in regulating beta-cell function: a novel mechanism in diabetes pathogenesis.

Reut Rifkind[1,2], Benjamin Glaser[2], Yuval Dor[1], Dana Avrahami[1,2]
[1]*Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel 91120*
[2]*Department of Endocrinology and Metabolism, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Israel 91120*

Type 2 diabetes (T2D), affecting over 425 million people worldwide, is driven primarily by pancreatic β-cell failure. While epigenetic regulation is critical for β-cell identity and function, the specific contributions of cytosine methylation (5mC) and hydroxymethylation (5hmC) remain poorly understood. This gap persists largely because conventional bisulfite-based approaches cannot distinguish between these two marks despite their distinct and often opposing regulatory roles. Our preliminary data analyzing several base-resolved 5hmC and 5mC maps generated using nanopore sequencing—which allows independent interrogation of 5hmC and 5mC profiles—from sorted β cells of HPAP donors show that 5hmC is highly enriched at active islet enhancers in endocrine cell types. In human β cells, 5hmC constitutes approximately 50% of all cytosine modifications, a level comparable to that observed in brain cells, whereas in most cell types 5hmC represents less than 5% of modified cytosines, consistent with a critical role for this mark in gene regulation. Additionally, in β cells from two T2D donors, 5hmC levels are reduced at the NKX2.2 locus, a key β-cell transcription factor, compared with non-diabetic samples. Furthermore, immunostaining of mouse and human pancreatic sections across multiple ages revealed an age-associated increase in β-cell 5hmC levels in both species, suggesting a conserved role for hydroxymethylation in postnatal β-cell maturation and maintenance. Based on these findings, we hypothesize that 5hmC is a key regulator of β-cell identity and function and that its disruption contributes to β-cell failure in T2D. To test this hypothesis, we will employ a genetic mouse model with β-cell-specific conditional ablation of the DNA demethylation enzymes TET2 and TET3 to define how loss of 5hmC disrupts postnatal β-cell maturation, identity, and function and how loss of 5hmC contributes to the development of T2D. Findings from this study will determine whether 5hmC plays a critical role in β-cell maturation and/or function and will establish a causal relationship between 5hmC loss and β-cell failure, providing a foundation for future epigenetic-directed therapeutic strategies for the prevention and treatment of T2D.

262

Endocrine Effects of Long-term Calcineurin Inhibitor Use in Solid Organ Transplant Recipients

Talia Diker Cohen[1,2], Idit Dotan[1,2], Bronya Calvarysky[3,4], Eyal Robenshtok[1,2]
[1]*Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Institute of Endocrinology, Diabetes and Metabolism*
[2]*Tel Aviv University, Tel Aviv, Israel, Gray Faculty of Medical and Health Sciences*
[3]*Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, Pharmacy*
[4]*The Hebrew University of Jerusalem, Jerusalem, Israel, Faculty of Medicine*

Background:
Calcineurin inhibitors (CNIs), mainly tacrolimus and ciclosporin, are the cornerstone of immunosuppression after solid organ transplantation. While essential for graft survival, long-term CNI exposure is associated with a wide range of endocrine and metabolic complications that are often under-recognized and inconsistently monitored.

Methods:
This is a narrative review of published clinical and mechanistic studies on endocrine effects of CNIs, complemented by expert clinical opinion derived from long-term multidisciplinary care of transplant recipients. Evidence was synthesized qualitatively without formal meta-analysis or evidence grading; where data were limited, recommendations reflect expert opinion rather than guideline statements.

Results:
CNIs disrupt endocrine homeostasis through inhibition of the calcineurin–NFAT pathway in non-immune tissues. Tacrolimus is consistently more diabetogenic than ciclosporin, impairing pancreatic β-cell function and increasing insulin resistance, thereby contributing to post-transplant diabetes mellitus. Both agents promote dyslipidemia and weight gain. CNIs accelerate bone loss by increasing osteoclast activity and impairing osteoblast function, leading to elevated early fracture risk. Renal magnesium wasting due to down-regulation of TRPM6/7 channels is common and often persistent, with downstream cardiovascular and metabolic implications. A functional hypoaldosteronism-like state with hyperkalemia and metabolic acidosis may occur, while overt adrenal insufficiency is uncommon but clinically relevant during stress or steroid withdrawal. Gonadal dysfunction is generally mild and reversible, thyroid effects are minimal, and emerging data suggest possible circadian rhythm and sleep disturbances. Based on these findings, a pragmatic framework for endocrine surveillance and management is proposed.

Conclusions:
Endocrine complications of CNIs are frequent, clinically significant, and potentially modifiable. Increased awareness and structured endocrine monitoring should be integrated into routine post-transplant care. Prospective studies are needed to validate screening strategies and optimize long-term outcomes.

263

The association between baseline cognitive function tests scores and physical capacity in older people with type 1 diabetes mellitus

Naama Peltz-Sinvani[1], Hagar Shimon[1], Yasmin Alt[1], Etay Cohen[1], Yael Keler[1], Nir Lasman[1], Jonathan Bleier[1], Amna Jabarin[1], Michal Azmon[1,2], Tali Cukierman-Yaffe[1,3]

[1]*The Center for Successful Aging with Diabetes, Division of endocrinology, diabetes and metabolism, Sheba Medical Center, Ramat-Gan, Israel*

[2]*The Physiotherapy Department, Faculty of Health Sciences, Ariel University, Ariel, Israel*

[3]*The Epidemiology Department, Gray School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*

Background and Aim

Cognitive disfunction is recognized as one of the long-term sequels of type-1 diabetes mellitus (T1DM).

Previous studies have demonstrated a bidirectional effect of hand grip strength on cognitive function and vice versa in middle-aged and older adults. Less is known with respect to other physical capacity tests.

The study`s aim is to delineate the association between cognitive function test score and physical capacity in older people with T1DM.

Methods

This analysis pertains to individuals with T1DM over the age of 60 years, who conducted assessments of cognitive (MOCA, DSST-digital, DSST- paper and pencil) and physical (hand grip test, STS, 6MWT, 10MW, TUG. FSST, BBS) health agility.

The relationship between indices of cognitive and physical health agility was assessed.

Results

Forty-one individuals with T1DM aged 70.0±4.6, 26 Females (63%), with 34.5±16.8 years diabetes duration, participated in this study. Mean HbA1c was 7.5±0.9%, TIR 63.1±14.7%. Twenty-seven (65.9%) participants had cognitive impairment (defined as a MOCA score 26). A significant correlation was demonstrated between an index of lower body strength (30sec STS) and scores achieved on a test pertaining to general cognitive capacity as well as executive function and psychomotor efficiency (DSST-digital and-paper and pencil, r= 0.327, 0.320; p= 0.037, 0.039, respectively). There was also a correlation between a measure of dynamic balance (FSST) and scores achieved on the DSST (paper and pencil, r= 0.361, p= 0.026) (Figure 1).

Conclusions

In older people with T1DM, there were correlations between measures of lower body strength, dynamic balance and a measure of general cognitive capacity, executive function and psychomotor efficiency.

	DSST-digital		DSST- paper and pencil	
	r	p-value	r	p-value
Handgrip strength	0.130	0.419	0.152	0.338
30sec_STS	**0.327***	**0.037***	**0.320***	**0.039***
6MWT	0.012	0.942	0.142	0.369
10m Walk	-0.003	0.986	-0.058	0.715
FSST	-0.274	0.100	**-0.361***	**0.026***

*Correlations were calculated based on Pearson Correlation Coefficient.

*DSST Digit Symbol Substitution Test, FSST four square step test, HbA1C hemoglobin A1C, MOCA Montreal cognitive assessment, TIR time in range, 6MWT six-minute walk test,10m Walk ten-meter walk, 30sec STS 30 second sit to stand test

Acknowledgement: This investigator-initiated study is supported by Medtronic, this was an unrestricted grant.

264

Nutritional Sources of Medium Chain Fatty Acids are Not Required For Ghrelin Acylation in Humans

Karin Later[1], Rachel Ben-Haroush Schyr[1], Khuloud Abu Tair[2], David Hakimian[3], Danny Ben-Zvi[1,4]

[1]*Department of Developmental Biology and Cancer Research, Institute for Medical Research Israel Canada, Hebrew University Of Jerusalem*

[2]*Department of Nutrition and Diet, Hadassah University Medical Center*

[3]*Institute of Gastroenterology and Liver Disease, Hadassah University Medical Center*

[4]*Center for Computational Medicine, Hebrew University Of Jerusalem*

Ghrelin is an orexigenic hormone secreted predominantly by gastric X-cells and is a potent stimulator of growth hormone release. Circulating ghrelin is suppressed after meals and rises during fasting. A subset of ghrelin molecules undergoes acylation with a medium-chain fatty acid (MCFA) within X-cells, a modification that is essential for binding and activation of the ghrelin receptor. As MCFAs are derived primarily from dietary sources, nutritional composition may critically influence ghrelin bioactivity.

Total parenteral nutrition (TPN) is known to suppress ghrelin secretion; however, a proportion of TPN-treated patients continue to experience hunger despite adequate caloric supply. We hypothesized that the lipid composition of TPN formulations, specifically their MCFA content, modulates circulating levels of total and acylated ghrelin and thereby affects appetite perception.

Nineteen hospitalized patients receiving TPN at Hadassah Medical Center for gastrointestinal diseases, postoperative complications, or gastrointestinal malignancies were enrolled. Eleven patients received SMOF (MCFA-rich) and eight received Triomel (MCFA-poor) formulations. Clinical parameters, plasma samples, and appetite scores were collected at baseline (fasting) and after one and two weeks of TPN, when applicable.

Preliminary analyses indicate that total ghrelin levels were not altered by TPN administration. However, SMOF treatment was associated with a three-fold increase in the fraction of acyl-ghrelin (p 0.05), whereas no significant change was detected in Triomel-treated patients. Furthermore, acyl-ghrelin levels were found to be lower in patients with a higher body mass index. Finally, a positive trend was observed between acyl-ghrelin levels and subjective hunger scores ($r = 0.438$), although this association did not reach statistical significance ($p = 0.117$).

The persistence of acyl-ghrelin in the absence of dietary MCFA in Triomel recipients suggests that X-cells may synthesize MCFAs de novo and/or maintain intracellular stores of acylated ghrelin. Nevertheless, the significant rise in acyl-ghrelin with SMOF implies that TPN lipid composition can modulate ghrelin acylation and potentially influence ghrelin-mediated hunger signalling.

265

Immune Activation and α-Cell Identity Remodeling Define Transcriptional States in Type 1 Diabetes

Haya Benhayon[1,2], Michael M Danziger[3], Danny Ben-Zvi[1,2], Michal Rosen-Zvi[2,3]
[1]*Institute of Medical Research Israel-Canada, the Hebrew University-Hadassah Medical School, Developmental Biology and Cancer Research*
[2]*the Hebrew University, Faculty of Medicine*
[3]*IBM Research – Israel*

Type 1 diabetes (T1D) is linked to physiological changes in α-cells, but the sequence of events leading this dysfunction, and the extent of α-cell heterogeneity in T1D remains unclear. Using single-cell transcriptomics of human pancreatic islets, we applied two complementary models: the IBM Biomedical Foundation Model (BMFM) and logistic regression, to identify T1D-associated transcriptional changes in α-cells.

BMFM consistently classified T1D through coordinated upregulation of α-cell-associated transcription factors, including MAFB, FOXO1, and MEIS2, observed across most patients and cells. This α-cell reinforcement contrasts with nonspecific dedifferentiation reported in mice, and suggests regulated identity remodeling, consistent with recent human studies in a different dataset. In contrast, logistic regression primarily identified immune and antigen-presentation genes (B2M, HLA class I), reflecting increased immune visibility rather than changes in endocrine function. Interestingly, most but not all α-cells in T1D displayed either patten, while a minority of α-cells in non-diabetic donors had transcriptional patterns characterizing α-cells in T1D patients.

Across cells and patients, immune-related genes and α-cell transcription factors were weakly negatively correlated, suggesting two possibilities: either a temporal sequence where α-cells first upregulate HLA genes in response to immune signaling or β-cell stress, and then enhance α-cell identity as β-cell repression is lost, or that these two processes occur in distinct α-cell subpopulations. Prior studies showing HLA enrichment near β-cells and immune infiltrates support context-dependent modulation of the α-cell transcriptome.

To test this, we are pursuing quantitative FOXO1 staining and pseudotime analyses anchored on antigen presentation genes to determine whether α-cell identity programs arise after, during or independent of immune activation. These results highlight that T1D involves both immune-driven stress responses and regulated α-cell identity remodeling, offering a nuanced view of disease-associated islet transcriptional states.

Intermittent Fasting and Body Composition in Older Adults: A Systematic Review and Meta-Analysis of RCTs

Assaf Gut[1], Assaf Buch[2,3], Naftali Stern[1,4], Keren Turgeman[1], Sharon Barak[5,6]
[1]*Grey faculty of medicine, Tel Aviv University*
[2]*The Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center.*
[3]*Faculty of Health Sciences, Ariel University, Department of Nutrition Sciences*
[4]*Sagol Center for Epigenetics, Aging Metabolism, Sourasky Medical Center*
[5]*Ariel University, Department of Nursing, Faculty of Health Sciences*
[6]*Pediatric Rehabilitation Department, Sheba Medical Center*

Background: The global rise in obesity among older adults (≥60 years) presents a complex clinical challenge. In this population, obesity is frequently characterized by a "sarcopenic" phenotype, where excessive adiposity- particularly visceral fat coexists with a progressive decline in skeletal muscle mass and quality. During weight loss interventions, the preservation of lean mass is paramount; excessive loss of fat-free mass can exacerbate functional impairment, increase frailty, and compromise metabolic health. While intermittent fasting has emerged as an effective weight-management strategy, its ability to promote fat loss while safeguarding critical lean tissues in older adults with overweight or obesity remains a subject of intense debate. To date, no systematic review has focused exclusively on the efficacy and safety of intermittent fasting in this high-risk demographic.

Objective: To systematically evaluate the effects of intermittent fasting on body weight, fat distribution, and lean/skeletal muscle mass in older adults (≥60 years) with obesity.

Methods: This systematic review and meta-analysis were conducted following PRISMA guidelines. Comprehensive searches were performed in Embase, MEDLINE, and Cochrane CENTRAL. Inclusion was restricted to RCT's with a mean participant age ≥60 and BMI ≥25 kg/m². Data synthesis utilized random-effects models, supplemented by subgroup analyses based on fasting protocol, comorbidities, and assessment modalities.

Results: Thirteen RCTs (n=768; mean age 63.5±7.7y) were synthesized. Three intermittent fasting protocols (5:2, Time-Restricted Eating, and Fasting-Mimicking Diet) were compared against continuous caloric restriction or usual care. Intermittent fasting was associated with a statistically significant reduction in body mass (SMD = −0.28, p=0.002), with the Fasting-Mimicking Diet showing the most pronounced effect (SMD = −0.56). Time-Restricted Eating demonstrated consistent efficacy in reducing BMI (SMD = −0.98), waist circumference (SMD = −0.39), and visceral fat (SMD = −0.57). Importantly, intermittent fasting did not lead to a statistically significant reduction in lean mass compared to controls (SMD = 0.17, p=0.15), suggesting a trend toward the preservation of fat-free mass. Subgroup analysis revealed that measurement techniques significantly influenced results, with BIA reporting larger effects on lean mass than DXA (p=0.04).

Conclusions: These findings provide the first meta-analytic evidence that intermittent fasting is a viable therapeutic tool for older adults facing obesity. By effectively targeting visceral adiposity while maintaining lean mass, intermittent fasting may mitigate the risks associated with sarcopenic obesity and promote robust functional aging. These results underscore the necessity of incorporating detailed body composition analysis rather than weight alone as a primary clinical outcome in geriatric nutritional interventions.

268

Deciphering liver glycome regulation by the PGC-1/FN3K axis and its significance

Idit Ron-Ronen[1], Efrat Glick-Saar[2], Amir Tirosh[1], **Neri Minsky**[1]
[1]*Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Sheba Medical Center*
[2]*Wohl Institute for Translational Medicine, Sheba Medical Center, Sheba Medical Center*

Background: Diabetes in general, and specifically in the context of obesity, is characterized by hyperglycemia resulting in non-enzymatic glycation of proteins. Yet, the full scope of molecular targets for glycation and its function, particularly in liver, are incompletely understood. De-glycation, which removes the attached sugars, is controlled intracellularly by fructosamine-3-kinase (FN3K). However, whether intracellular de-glycation is regulated in physiological contexts and what factors and functions are involved in its regulation remain unknown.

Study Aim: To identify factors controlling the regulation of FN3K and protein glycation in liver, and to elucidate the targets of that regulation and its potential involvement in cellular pathways.

Methods: Gene expression analysis in mouse liver and cell culture experiments with overexpression of the key metabolic regulators PGC-1s (PGC-1α and PGC-1β). Mass spectrometric analysis was used to monitor protein glycation.

Results: Our data identify that regulation of protein glycation in liver is controlled by the key metabolic regulators PGC-1s in response to metabolic cues. Liver-specific deletion of PGC-1s results in global changes in gene expression as determined by RNA-sequencing, among which is reduction of Fn3k expression and concomitant increase in specific protein glycation. Overexpression of PGC-1a in primary hepatocytes and in liver-derived cell lines induces Fn3k mRNA and protein levels and reduces protein glycation. In human liver cancer samples, expression of Fn3k mRNA is significantly correlated with PGC-1α mRNA expression. Purification of glycated proteins followed by mass spectrometric analysis and subsequent validations reveal significant alterations in intracellular protein glycation in response to PGC1-α expression in mouse liver and in cultured cells. Mechanistically, PGC-1α effect on Fn3k is transcriptional, and a fragment from the Fn3k gene is identified as a regulatory element mediating the effect. Finally, PGC-1α effects on mitochondrial respiration are shown to be affected by cellular FN3K levels.

Discussion: Our study demonstrates that in liver, fasting and re-feeding govern intracellular protein glycation via PGC-1 dependent induction of FN3K. Our work establishes the PGC1/FN3K axis as a key regulator of protein glycation.

Study Importance: Our work reveals protein glycation as a regulated process, revealing the scope and dynamic nature of the liver glycome, as well as its potential involvement in mitochondrial respiration.

270

Mitochondrial Phosphorylation as a Metabolic Switch: The Role of CPS1 in Glucagon-Driven Urea and Glucose Regulation

Hadar Bar Dagan[1], Yuval Adar[1], Nofar Halimi[1], Kfir Sharabi[1]
Institute of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem

The liver plays a pivotal role in maintaining whole-body energy homeostasis in response to the nutritional and hormonal changes associated with fasting and feeding. An essential hormone in regulating liver metabolism is glucagon, which mobilizes glycogen and promotes gluconeogenesis and fatty acid oxidation to maintain homeostatic blood glucose concentrations. Hyperglucagonemia is also observed in diabetic patients and significantly contributes to the associated hyperglycemia. The molecular effects of glucagon in hepatocytes have been studied in great detail and focus mainly on the cytoplasmic targets of PKA that initiate the transcription of key metabolic genes and control the activity of key metabolic enzymes. Surprisingly, very little attention is given to the direct molecular effects of glucagon on mitochondria function, despite glucagon's robust effect on mitochondria activity and the crucial role mitochondria play in the adaptive response to glucagon. Following phosphoproteomic analysis of mitochondria isolated from glucagon-injected mice, we identified novel phosphosites in several key metabolic pathways. Importantly, we identified phosphosites on key enzymes of the urea cycle, and show that mutating these sites alters enzyme activity. We propose that glucagon acutely regulates flux through the urea cycle to coordinate nitrogen disposal and glucose metabolism in the postabsorptive state. This study will highlight a molecular aspect of how mitochondria respond to glucagon and will improve our knowledge of this crucial response.

271

The effects of gut microbiome-derived metabolites on hepatic glucose metabolism

Or Maalumi[1], Or Blank[1], Julius Ben-Ari[1], Kfir Sharabi[1]
Biochemistry, Food science and nutrition, Hebrew university of Jerusalem

Type 2 diabetes (T2D) is a global epidemic, with an increasing prevalence. It is a chronic metabolic disease characterized by elevated fasting hyperglycemia, primarily due to excessive hepatic glucose production. When not controlled, T2D can lead to life-threatening microvascular and macrovascular complications. In recent years, microbiome-derived metabolites have been linked to health and disease states and have gained much interest as potential therapeutic agents. Indole-3-propionic acid (IPA), a metabolite produced exclusively by the gut microbiome through the catabolism of the essential amino acid tryptophan, has been linked to beneficial effects on human physiology. Among these effects, IPA has also been shown to be inversely associated with the severity of T2D in humans. However, the molecular mechanism by which IPA elicits its beneficial effects is still unknown. We hypothesize that IPA directly affects hepatocytes to regulate their metabolic function in a manner that would be metabolically beneficial to the whole organism. We test this hypothesis using isolated mouse primary hepatocytes and discovered that IPA can directly inhibit glucose production in hepatocytes, which is also associated with reduced expression of gluconeogenic genes. Metabolomic analysis revealed the accumulation of intermediary metabolites from the urea cycle and TCA cycle, suggesting that altered flux through these cycles mediates the metabolic effect of IPA. We found that IPA reduces the activity of the urea-cycle rate-limiting enzyme, CPS1. Preliminary in vivo studies also suggest that acute treatment of diabetic mice with IPA can improve glucose tolerance, suggesting that IPA can be used as a potential antidiabetic treatment.

Impaired glucose homeostasis in telomouse, a novel mouse model with short-telomeres

Moshe Sellam[1,2], Kamil Bar-Nes[1,2], Riham Smoom[3], Reut Rifkind[1,2], Benjamin Glaser[2], Yehuda Tzfati[3], Dana Avrahami[1,2]

[1]*Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel*

[2]*Department of Endocrinology and Metabolism, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel*

[3]*Department of Genetics, The Silberman Institute for Life Sciences, The Hebrew University of Jerusalem.*

Telomere shortening, a hallmark of aging, has been associated with metabolic decline and type 2 diabetes (T2D), yet the underlying mechanisms remain poorly understood. We hypothesized that short telomeres negatively impact age-related metabolic parameters and accelerate the development of T2D.

As wild-type (WT) mice possess very long telomeres, they are not suitable for studying the link between telomere length and metabolic decline. Therefore, we used the Telomouse model featuring a point mutation in the Rtel1 gene that results in human-length short telomeres and examined metabolic phenotypes with age and under metabolic stress induced by a high-fat diet (HFD).

We show that Telomice are insulin resistant as early as 4 months of age, as assessed by insulin tolerance testing (ITT; AUC, p0.001), and exhibit increased body weight compared to WT mice (mean 28.5 g vs. 26.2 g, p=0.002). Glucose homeostasis worsened with age, reflected by slower glucose clearance at 16 months (GTT AUC, p0.001) and elevated fasting glucose levels (mean 107.6 mg/dL vs. 80.9 mg/dL, p0.0001). Pancreatic β cells displayed a compensatory response, with increased β-cell mass (0.053 vs. 0.035 mg/gr body weight, p0.05) and elevated plasma insulin levels in vivo (2.75 ng/mL vs. 1.64 ng/mL, p=0.0035; n=6–9 mice), ruling out primary β-cell dysfunction as the cause of dysregulation. A pyruvate tolerance test in fed mice revealed increased glucose production (PTT AUC, p=0.003; n=8–10 mice per group), pointing to a hepatic contribution to insulin resistance. Consistently, Western blot analysis of hepatic insulin signaling targets showed impaired AKT phosphorylation (Ser473/Thr308), reduced glycogen synthase inhibition, and decreased mTORC1 activity in Telomice. Notably, under HFD conditions, Telomice regained insulin sensitivity after two months, leading to slower diabetes progression compared to WT mice. Gene set enrichment analysis (GSEA) of liver RNA sequencing data revealed enrichment of cell cycle and apoptosis pathways, suggesting increased hepatocyte turnover, along with enhanced inflammatory signatures, which were validated by immunostaining. In parallel, metabolic gene sets were downregulated in Telomice, collectively indicating an augmented hepatic response to diet-induced metabolic stress. To summarize, these findings support the hypothesis that short telomeres accelerate age-related metabolic decline and establish the Telomouse as a valuable model for investigating the role of telomere biology in age-related metabolic disease.

273

New Aspects of Beta Cell Physiology Revealed by mTOR Signaling

Ronny Helman[1]
Institute of Biochemistry, Food Science, and Nutrition, The Hebrew University

Pancreatic beta cells regulate glucose homeostasis by balancing insulin secretion with the prevention of cellular exhaustion. This study introduces a comprehensive framework for beta cell function, demonstrating that this balance is achieved through population-level heterogeneity and intrinsic molecular feedback mechanisms. Phosphorylated S6 (pS6) serves as a functional marker, showing that beta cells are sequentially recruited as glucose concentrations increase, with high-capacity cells located in the islet core. The mechanistic target of rapamycin complex 1 (mTORC1) is identified as a rapid intrinsic sensor of beta cell activity. Notably, mTORC1 functions as a negative feedback regulator: upon activation by the secretory machinery, it restricts vesicle trafficking, thereby preventing excessive insulin release. This incoherent feedforward loop enables beta cells to generate a robust insulin response while autonomously mitigating the risk of hypoglycemia. Collectively, these results highlight a division of labor and an intrinsic feedback system that protect metabolic health.

274

A clinical scoring system to guide genetic evaluation in pediatric obesity

Hanna Ludar[1], Shira London[1,2], Inbal Halabi[1,3], Keren Cohen[1], Majdoub Hussein[1], Ghadir Elias-assad[4,5], Ilana Koren[1]

[1]*Pediatric Endocrine and Diabetes clinic, Clalit Health Services, Haifa and west Galili District, Israel*

[2]*Pediatric Endocrine and Diabetes Unit, Rambam medical center*

[3]*Pediatrics unit, Carmel medical center*

[4]*Pediatric Endocrine Clinic, Clalit Health Services, Northern region, Israel*

[5]*Pediatric Endocrine Institute, Saint Vincent Hospital, Nazareth, Israel*

Background:

Monogenic and syndromic etiologies account for a small but clinically important subset of pediatric obesity. Establishing a precise genetic diagnosis has important implications for clinical follow-up and treatment. However, tools to guide referral for genetic evaluation are limited.

Methods:

Between August 2021 and December 2023, children with obesity underwent genetic testing as part of the Rhythm Monogenic Obesity Study. A phenotype-based clinical scoring system was developed to guide study enrollment. Genetic results were available for 91 of 93 tested patients. We evaluated the association between score category (high score ≥9 vs. low score <9) and genetic findings, as well as clinical characteristics across genetic result groups.

Results:

Genetic variants were identified in 71% of patients with a high clinical score (≥9) compared with 50% of those with a low score (<9) (P=0.044). Pathogenic or likely pathogenic variants were more frequent in the high-score group (25% vs. 15%), whereas benign variants were more common in the low-score group (42% vs. 32%).

When comparing patients with pathogenic variants to those with variants of uncertain significance, benign variants, or no identified variant, no significant differences were observed in birth weight, BMI, age at onset of weight gain, hyperphagia, family history of obesity, or total clinical score. Obesity-related complications were highly prevalent across all groups, with 87.5–100% of patients in each group presenting with at least one complication, without significant differences between groups.

Conclusions:

A higher clinical score was associated with increased detection of genetic variants and showed a trend toward a higher proportion of pathogenic findings. However, clinical characteristics alone did not reliably distinguish patients with pathogenic variants from those without. This scoring system may aid in prioritizing patients for genetic evaluation while highlighting the phenotypic overlap among patients with genetic and non-genetic pediatric obesity.

275

Successful levothyroxine discontinuation in patients with a persistently normal TSH

Ori Adler[1], David Fisher[2,3], Tamar Freud[4], Howard Tandeter[4], Merav Fraenkel[2,3]
[1]*Internal Medicine B, Soroka University Medical Center*
[2]*Endocrinology, Soroka University Medical Center*
[3]*Faculty of Health Science, Ben Gurion University of the Negev*
[4]*Department of Family Medicine and Siaal Research Center for Family Medicine and Primary Care, Ben-Gurion University of the Negev*

Background

Levothyroxine is widely prescribed for subclinical and overt hypothyroidism yet in some patients the indication for lifelong therapy remains uncertain. This study assessed whether long-term levothyroxine therapy can be safely discontinued in patients with persistently normal thyroid function. Secondary objectives were to identify predictors of successful levothyroxine discontinuation.

Methods

This prospective cohort study included adults (≥18 years) treated with levothyroxine for ≥5 years who had maintained a normal annual TSH for five consecutive years. Eligible patients were identified through a computerized search of electronic medical records of Clalit Health Services, Southern District. Exclusion criteria included prior thyroidectomy, radioactive iodine therapy, diagnosis of congenital hypothyroidism or women with childbearing potential.

After obtaining informed consent, demographic data and baseline clinical, biochemical (including anti-thyroid peroxidase (TPO) antibodies) and current levothyroxine dose were recorded. Levothyroxine was discontinued, and participants were followed for 24 weeks with thyroid function tests and clinical assessments for symptoms of hypothyroidism at 4, 10, 16, and 24 weeks.

Treatment was restarted if during follow-up one of the following occured:

TSH 10 mIU/L and/or free T4 below the lower limit of normal
Symptoms of hypothyroidism developed
The primary outcome was resumption of levothyroxine. Hazard ratios (HRs) for levothyroxine reinitiation were calculated using Cox proportional hazards models.

Results

Eighty-three patients were enrolled (69 women, 83%), mean age of 70.5 ± 9.1 years; 32 were anti-TPO seropositive, 45 were seronegative and in 6 patients antibody status was not available. As of January 2026, sixty-seven patients completed 24-weeks follow-up; 33 patients (49.3%) remained biochemically and clinically euthyroid. Thirty-four patients (50.7%) required levothyroxine resumption: 23 (34%) due to biochemical hypothyroidism and 11 (16.4%) due to clinical hypothyroidism (of these patients, 6 had subclinical hypothyroidism and 5 were biochemically euthyroid).

Mean time to levothyroxine resumption was 6.4 ± 4.8 weeks (median 4 weeks). Following multivariable analysis adjusted for age, sex, and duration of prior euthyroid status, only levothyroxine dose (µg/kg) at study entry independently predicted treatment resumption (HR 5.1, 95% CI 1.65–15.63; p = 0.005). No serious adverse events were observed.

Conclusions

Half of patients receiving long-term levothyroxine with biochemical control were able to discontinue therapy and remain euthyroid after 24 weeks. The need for treatment resumption occurred early in those who failed discontinuation and was predicted by a higher baseline levothyroxine dose at study entry. Supervised levothyroxine withdrawal is feasible and safe in selected patients and may reduce unnecessary long-term treatment.

276

Adipocyte hypertrophy in visceral, not subcutaneous, adipose tissue associates cross-sectionally with poor obesity phenotype and predicts better response to bariatric surgery

Marina Rosengarten Levin[1,2], Hadar Klein[3], Yulia Haim[1], Alexandra A. Tsitrina[1,4], Habib Mualem[1], Alon Zemer[1], Oleg Zilber[1], Yair Pincu[1], Idit F. Liberty[5], Oleg Dukhno[6], Nur Alkrinawi[6], Iris Shai[3], Assaf Rudich[1], Uri Yoel[1,7]

[1]*Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

[2]*Maccabi Health Care Services, Rehovot, Israel*

[3]*The Health &amp Nutrition Innovative International Research Center, Department of Epidemiology, Biostatistics and Community Health Sciences, Faculty of Health Sciences, School of Public Health, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

[4]*Ilse Katz Institute for Nanoscale Science and Technology*

[5]*Diabetes Clinic*

[6]*Surgical word B*

[7]*Endocrinology, Soroka University Medical Center, Beer-Sheva, Israel*

Introduction: The etiology of the obesity pandemic remains unclear, but obesity's link with cardiometabolic Adiposity Based Chronic Diseases is strongly reflected/mediate by how adipose tissue adapts to chronic caloric excess. Cross-sectional evidence indicates that adipocyte hypertrophy associates and may contribute to metabolically-complicated obesity. Here we hypothesized that this adipose tissue features also predict treatment response.

Methods: We established a prospective database integrating histopathological features of subcutaneous (SAT) and visceral (VAT) adipose tissue obtained during bariatric surgery, coupled with clinical data. Participants were followed-up 6 and 12 months post-surgery. Ninety-one individuals (predominantly women) were enrolled with complete histopathological, and 12-months follow-up data is now available for 31.

Results: A trend-line connecting mean adipocyte size (estimated in histological sections) with BMI in SAT and VAT defined four phenotypes: Double-Hypertrophic, Hypertrophic VAT-only, Hypertrophic SAT-only, and Double-Hyperplasic. The two VAT-hypertrophic groups had higher metabolic syndrome parameters than double-hyperplastic and the SAT-only hypertrophic groups. Similarly, prediabetes was more prevalent (46.9 and 30.8%) in the two VAT-hypertrophic groups than the other two groups (16.7 and 12.8%), and similar trends were cross-sectionally observed for liver enzymes. Importantly, among n=31 for whom 12-months follow-up data is available, %-weight loss was higher among the two VAT-hypertrophic groups than the two groups with hyperplastic VAT adipocytes (~35 vs. 23%). Consistently, only VAT estimated adipocyte size correlated with greater % weight loss 12-months following surgery (r-0.460, p=0.012).

Conclusions: VAT, not SAT, adipocyte hypertrophy is an adipose tissue feature cross-sectionally associated with more complicated obesity, that also predicts improved response to bariatric surgery.

277

A Mechanistic Model for the Cortisol Paradox in PTSD

Yaniv Grosskopf[1], Dor Danan[1], Yoav Hayut[1], Yoel Toledano[2], Keren Doenyas-Barak[3], Avi Mayo[1], Uri Alon[1]

[1]*Department of Molecular Cell Biology, Weizmann Institute of Science*

[2]*Rabin Medical Center*

[3]*Shamir Medical Center*

Post-Traumatic Stress Disorder (PTSD) is a devastating disease whose mechanisms are not fully understood. A longstanding biological paradox in PTSD is the low basal cortisol levels seen in most studies, despite the expectation of elevated cortisol under chronic stress. This "low cortisol paradox" challenges traditional hypothalamic-pituitary-adrenal (HPA) axis models. Cortisol is low despite normal levels of its upstream regulator ACTH in PTSD patients, and individuals with PTSD exhibit blunted hormonal responses to acute stress. To understand this dysregulation, we apply a previously calibrated mathematical model of the HPA axis that incorporates dynamic changes in gland functional mass of the pituitary corticotrophs and adrenal cortex. We model individuals with PTSD by changing a single parameter - elevated glucocorticoid receptor (GR) sensitivity, a known risk factor for PTSD. We show that elevated GR sensitivity leads to low cortisol and normal ACTH, reconciling key clinical observations. Low cortisol despite normal ACTH is due to a reduced adrenal functional mass, consistent with PTSD animal experiments. The model also recapitulates the blunted responses to acute stress and the dexamethasone/ corticotropin-releasing hormone (Dex/CRH) test reported in PTSD cohorts. Importantly, the model turns the cortisol paradox on its head - despite low cortisol levels, GR activity is higher than normal due to the enhanced sensitivity. Thus, individuals with PTSD experience elevated GR signaling despite their low cortisol levels. The model quantitatively predicts the reduction in morning serum cortisol in a large medical database from thousands of individuals diagnosed with PTSD, without the need to fit parameters. These findings provide a unified mechanistic explanation for HPA axis dysregulation in PTSD.

279

Thyroid Cancer in the Elderly- Specific Clinical and Histopathological Characteristics and Treatment Considerations- A Retrospective Cohort Study

Uri Yoel[4,5], **Liroy Caracucli**[1], Daphna Idan[1], Natalya Bilenko[2], David Shacham[3,4]
[1]*The Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[2]*Department of Epidemiology, Biostatistics and Community Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
[3]*Geriatric department, Soroka University Medical Center, Beer-Sheva, Israel*
[4]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
[5]*Endocrinology Unit, Soroka University Medical Center, Beer-Sheva, Israel*

Background
Age is an integral part of differentiated thyroid cancer (DTC) staging, yet data on patients ≥65 years remain limited. We investigated whether elderly patients demonstrate more adverse histopathology findings, receive different therapy compared with younger patients, and have worse outcomes.

Methods
We conducted a retrospective cohort study of adults with histologically confirmed DTC (2013–2024), grouped by age at diagnosis: 18–54, 55–64, and ≥65 years. We compared baseline characteristics, histopathological features, treatment and follow-up patterns using groupwise tests and age trends (Kendall's tau; Ptrend). Endpoints were one-year response to therapy, disease-free survival (DFS), and progression-free survival (PFS). Multivariable analyses estimated adjusted associations of older age with (1) high-risk category according to the American Thyroid Association (ATA) guidelines using logistic regression (odds ratios (OR), 95% CIs); and (2) DFS and PFS using Cox models (hazard ratios, 95% CIs), adjusting for relevant covariates. Two-sided P 0.05 denoted significance.

Results
We included 323 patients (199 aged 18–54, 57 aged 55–64, and 67 aged ≥65 years). The median follow-up was 36.5 months. Adverse pathology increased across age groups: aggressive PTC variants 6.0%, 12.3%, 23.9% (Ptrend 0.001); any extrathyroidal extension (ETE) 20.6%, 28.1%, 47.8% (Ptrend 0.001); vascular invasion 17.1%, 7.0%, 32.8% (Ptrend = 0.078); bilateral lateral-neck lymph node metastases 3.0%, 5.3%, 10.4% (Ptrend = 0.022); distant metastasis 1.5%, 5.3%, 10.4% (Ptrend = 0.0014). Accordingly, rates of ATA high-risk category increased with age 6.5%, 10.9%, 34.8% (Ptrend 0.001; P [55-64 vs ≥65] =0.003). A higher proportion of elderly patients received 150 mCi of radioiodine: 18.5%, 15.7%, 38.8% (Ptrend = 0.016; P [55–64 vs ≥65] = 0.038). In multivariable analysis, older age was independently associated with high-risk ATA category, with each additional year increasing the likelihood by 5.9% (adjusted OR 1.059, 95% CI 1.030–1.090, P 0.001), while response to therapy, DFS, and PFS remained comparable across age groups.

Conclusions
Adverse histopathological features and high-risk ATA category increased with increase in age group with the highest prevalence in patients aged ≥65 years. Nevertheless, one-year response, DFS, and PFS were comparable across groups following appropriate treatment. These findings support risk-adapted management in elderly patients and suggest that age alone should not limit treatment intensity.

280

NME3 as a Mediator of the Glucagon–Mitochondria Axis in Hepatic Metabolism and Type 2 Diabetes

Naama Miron Meir[1], Bar Avni[1], Sonya Basin[1], Kfir Sharabi[1]
The Institute of Biochemistry, Food Science and Nutrition, The Hebrew University of Jerusalem, Israel

Glucagon is a central regulator of hepatic glucose and lipid metabolism, yet its direct effects on mitochondria remain poorly understood. This gap is striking given the essential role of mitochondria in gluconeogenesis, fatty acid oxidation, and ureagenesis, pathways that are disrupted in type 2 diabetes (T2D). Our preliminary data identify nucleoside diphosphate kinase 3 (NME3), a poorly studied outer mitochondrial membrane protein, as a novel glucagon-inducible regulator of mitochondrial dynamics and quality control in hepatocytes. We show that glucagon stimulation increases NME3 protein level, whereas hepatic Nme3 depletion lowers fasting glycemia, alters lipid profiles, and induces mitochondrial fragmentation. Mechanistically, Nme3 knockdown reduces ATF4 protein levels, impairs glucagon-induced autophagy, and changes the abundance of mitochondrial complex IV, implicating NME3 as a critical mediator of stress signaling and mitophagy.

The novelty of this work lies in uncovering a glucagon–mitochondria axis mediated by NME3, providing a mechanistic link between hormonal cues and mitochondrial adaptation in hepatocytes. Because excessive hepatic glucose production and mitochondrial dysfunction are defining features of type 2 diabetes (T2D), these findings offer a new perspective on disease pathogenesis. Furthermore, as dual GLP-1/glucagon agonists are emerging as promising therapies for obesity and diabetes, clarifying glucagon's mitochondrial actions offers immediate translational relevance. Together, our data establish NME3 as a central node connecting glucagon signaling to mitochondrial quality control, with broad implications for the treatment of metabolic diseases.

281

SDF-1 Mediates Liver Metabolic Adaptation Through CXCR7: Implications for MASH Pathogenesis

Rachel Barkan Michaeli[1], Chaim Atay Fainshtein[1], Hadar Bar-Dagan[1], Nof Hadar[1], Kfir Sharabi[1]

The Institute of Biochemistry, Food Science, and Nutrition, The Robert H. Smith Faculty of Agriculture, The Hebrew University in Jerusalem

Background and aims:
The liver is a central metabolic organ crucial for whole-body glucose and lipid regulation, and its dysregulation is implicated in type 2 diabetes (T2D) and the progression from metabolic dysfunction-associated steatotic liver disease (MASLD) to metabolic dysfunction-associated steatohepatitis (MASH). This study aimed to elucidate the role of stromal cell-derived factor 1 (SDF-1) and its receptors CXCR4 and CXCR7 in hepatic metabolic adaptation and lipid homeostasis. While SDF-1 is well-known for its role in liver injury responses, its involvement in the metabolic adaptation of the liver remains unclear.
Materials and methods:
We employed a combination of mouse genetics, diet-induced obesity model, and primary hepatocyte cultures. Hepatocytes-specific SDF-1 knockout mice (n=8-10 per group) were compared with control littermates following a Western diet feeding; additionally, hepatocyte-specific overexpression of CXCR7 or CXCR4 was achieved via adenoviral vectors. Quantitative PCR, histological fat quantification, and standard biochemical assays were performed.
Results and Conclusion:
Our findings demonstrate that glucagon stimulation of primary hepatocytes robustly upregulated ACKR3/CXCR7 expression by approximately 10-fold (p0.001), while insulin treatment suppressed CXCR4 expression by about 50% (p0.01). In vivo, SDF-1 expression was significantly elevated in the refed state, and both SDF-1 and ACKR3 were markedly dysregulated in mice fed a Western diet (p0.05). Hepatocyte-specific depletion of SDF-1 led to a ~50% increase in hepatic fat accumulation (p0.05), and hepatocyte-specific overexpression of CXCR7 produced a comparable increase in hepatic lipid content. In contrast, overexpression of CXCR4 had no significant effect. The impact of the SDF-1 axis on lipid metabolism appears to be cell-autonomous, as overexpression of CXCR7 in isolated hepatocytes also resulted in increased fat accumulation. Mechanistically, mTORC1 signaling is altered when CXCR7 is overexpressed, linking the SDF-1 axis to lipid metabolism. Together, these data highlight a central role for SDF-1, primarily via the CXCR7/ACKR3 axis, in regulating hepatic lipid homeostasis and metabolic adaptation. Targeting this pathway may offer novel therapeutic opportunities for managing liver metabolic dysfunction and preventing the progression of MASH.

282

12:12 time-restricted feeding corrects weight cycling -induced aggravation of glucose intolerance and circadian disruption in young mice

Habib Muallem[1], Alon Zemer[1], Yulia Haim[1], Marina Rosengarten-Levin[1], Yuval G. Noach[1], Alexandra Tsitrina[2], Uri Yoel[1], Hiroshi Tsuneki[3], Tsutomu Wada[3], Toshiyasu Sasaoka[3], Alon Monsonego[4], Assaf Rudich[1]

[1]*Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

[2]*Ilse Katz Institute of Nanoscale Science and Technology, Ben- Gurion University of the Negev, Beer-Sheva, Israel*

[3]*Department of Clinical Pharmacology, University of Toyama, Toyama, Japan*

[4]*The Shraga Segal Department of Microbiology, Immunology and Genetics, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

Introduction: Weight gain-loss-regain cycle(s) (weight cycling, WC) is increasingly common in obesity due to the high prevalence of weight-loss attempts and the difficulty to maintain weight loss. Reported health impacts of WC compared to persistent obesity (PO) are inconsistent, particularly in the post-weight-loss obese state (PWLO), and in different age-groups. Here we hypothesized that WC induces age-distinctive metabolic, inflammatory and circadian regulatory responses in obesity.

Methods: Young (7 weeks) and mid-age (1 year) old male mice were subjected to a 15-week ad-libitum dietary intervention, wherein persistently lean (PL) and PO mice were fed normal-chow or high-fat diets, respectively, throughout. PWLO underwent one cycle of weight-loss and full regain, and late-onset obese (LO) were fed high-fat diet only during the second weight gain phase (weeks 11-15).

Results: Obesogenic memory in the lean state, manifesting by a higher initial weight regain rate compared to the initial weight-gain in same and LO mice was evident in young, but not mid-age. Furthermore, PWLO only in young mice worsened glucose tolerance compared to other obese groups. This associated with attenuated active/inactive-phase circadian oscillation (of locomotion, energy expenditure, feeding duration), exacerbated obesity-associated blunting of adipose, liver and hypothalamus core clock genes' regulation, and increased hepatic GNG gene expression. In mid-age, the identical dietary protocol resulted in milder dysglycemia, less pronounced circadian oscillation blunting and a lower inflammatory response of adipose tissue. Importantly, 12:12 time-restricted feeding corrected the aggravated glucose intolerance and circadian disruption induced by weight cycling in young mice.

Conclusion: WC differentially affects young and mid-aged mice in the obese state. Young mice display greater vulnerability to weight (re)gain, glucose intolerance and disruption of the circadian regulation of feeding. TRF seems to entrain circadian rhythmicity and improve glucose tolerance in young mice.

283

Adolescent to Adulthood Weight Trajectories and the Risk of Cancers

Cole Bendor[1], Aya Bardugo[1], Avishai Tsur[1], Estela Derazne[2], Itay Shemesh[3], Lotmit Bourvine, Dror Dicker[4], Ben Boursi[5], Amir Tirosh[5], Arnon Afek[5], Ran Rotem[6], Gabriel Chodick[2], **Gilad Twig**[5]

[1]*Israel Defense Forces*

[2]*Tel-Aviv University*

[3]*Novo Nordisk*

[4]*Rabin Medical Center*

[5]*Sheba Medical Center*

[6]*T.C. Chan School of Public Health, Harvard University, MA, USA*

Background: High BMI is a modifiable cancer risk factor, projected to surpass smoking as the leading preventable risk factor. The impact of weight change from late adolescence to adulthood on cancer risk remains unclear. We aimed to assess the association between adolescence-to-adulthood BMI trajectories and obesity-related cancer risk.

Methods: A population-based cohort study of 800,024 people insured by a large state-mandated health provider. BMI was measured during military pre-recruitment evaluations in adolescence and in subsequent clinic visits in adulthood. Follow-up began one year after an adult BMI measurement until cancer diagnosis, death, transfer to another health provider, or December 16, 2021. BMI trajectories from adolescence to adulthood were classified as lean-to-lean, lean-to-high, high-to-lean, and high-to-high (cutoff: 85th percentile in adolescence, 25 kg/m2 in adulthood). Weight change was also assessed per 5% increments. The primary outcome was obesity-related cancers including esophagus, postmenopausal breast, liver and gallbladder, stomach, pancreas, colon and rectum, kidney, multiple myeloma, thyroid, uterus and ovary. The secondary outcome was set as obesity-related cancers diagnosed before age 50 years (early-onset cancers). Cox proportional hazards models were applied.

Findings: During 7,610,263 person-years, 6,376 people were diagnosed with obesity-related cancers, at a mean age of 53.3±9.8 years. Adjusted HRs were 1.31 (95% CI 1.24–1.39) for lean-to-high, 1.01 (95%CI 0.78–1.31) for high-to-lean, and 1.47 (95%CI 1.34–1.61) for high-to-high groups, compared to the lean-to-lean group. Each 5% weight gain conferred a 3% increased hazard (95%CI 1.02–1.03). Findings persisted for early-onset cancers.

Interpretation: Maintaining a healthy BMI from adolescence to adulthood may reduce obesity-related cancer risk, including early-onset, highlighting the importance of early weight management strategies.

*Part of the content was just published in January 2026 (eClinicalMedicine, Volume 91, 103711).

Mechanisms of Aldolase B mediated beta cell glucotoxicity

Loren Jubran[1,2], Dana Avrahami[1,2], Benjamin Glaser[1]
[1]*Department of Endocrinology and Metabolism, Hadassah-Hebrew University Medical Center Jerusalem, Israel*
[2]*Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel*

Background: Diabetes is associated with β-cell dysfunction attributed to the toxic effects of chronic hyperglycemia (glucotoxicity). Initially, elevated glucose promotes β-cell proliferation, but prolonged exposure leads to dysfunction and loss of replicative capacity. Among glycolytic enzymes, Aldolase B (AldoB) is the most upregulated in human and rodent β-cells exposed to high glucose. AldoB is a key enzyme in hepatic glucose and fructose metabolism but is normally expressed at low levels in β-cells. Although several studies have proposed mechanisms through which AldoB could affect β-cell function, causality has not been demonstrated.
Methods and Findings: To test the hypothesis that AldoB mediates glucotoxic effects on β-cells, we analyzed single-cell transcriptomes from diabetic mice. AldoB-positive β-cells showed upregulation of pentose phosphate (PPP) and polyol pathway genes and downregulation of respiration-related genes. Glucose-stimulated insulin secretion (GSIS) assays using AldoB knockout (KO) and wild-type (WT) islets pre-incubated for 48 h in normal (11.8 mM) or high (30 mM) glucose revealed similar stimulated insulin release but higher basal secretion in AldoB-expressing islets, reducing the stimulation index. Western blot and FACS analyses showed reduced mTORC1 signaling (pS6) in KO islets under high glucose. Furthermore, β-cells expressing AldoB exhibited decreased proliferative capacity under high-glucose conditions. Metabolomic profiling revealed increased glycolytic and TCA intermediates in AldoB-expressing islets.
Conclusions: Our findings suggest that AldoB mediates β-cell overactivation, characterized by enhanced glycolysis, mTORC1 hyperactivation, increased basal insulin release and reduced proliferation, while its ablation blunts these effects and preserves GSIS and proliferative capacity, indicating that AldoB upregulation in β-cells worsens glucotoxic effects.

285

Sustained Hyperglycemia Induces Senescence in Osteocyte-Like Cells

Natan Lishinsky-Fischer[1], Irina Gurt[2], Vladislav Temkin[2], Joshua Stokar[1,2], Rivka Dresner-Pollak[1,2]

[1]*The Faculty of Medicineת Hebrew University of jerusalem, Israel*

[2]*Department of Endocrinology and Metabolism, Division ofMedicine, Hadassah Medical Organization, Jesrusalem, Israel*

Skeletal fragility with fractures is a serious complication of type 1 (T1D) and type 2 diabetes (T2D). Hip fracture risk is six-fold higher in T1D compared with age- and sex-matched non-diabetic controls. Although diabetic complications affecting the vasculature, brain, eyes, nerves, and kidneys are well recognized, bone fragility received less attention, despite hip fractures being associated with substantial morbidity and mortality. Current therapies to reduce fracture risk in diabetes are limited. As diabetic patients live longer, there is an urgent need to identify new therapeutic targets. Diabetes is a state of accelerated aging, and cellular senescence is a fundamental aging mechanism. Senescent cells cease proliferation, resist apoptosis, and develop a senescence-associated secretory phenotype. Moreover, clearance of senescent cells was shown to improve bone health in mouse models of osteoporosis. The osteocyte is the longest-lived cell in bone, an orchestrator of bone formation and resorption, and was shown to play a key role in diabetes-associated skeletal fragility. We investigated whether hyperglycemia induces osteocyte senescence in vitro.

IDG-SW3 osteocyte-like cells were induced to osteogenesis and cultured for 28 days under: normal glucose (NG; 5 mM), high glucose (HG; 25 mM), and osmotic control (mannitol 20 mM plus glucose 5 mM; MAN). Protein profiling was performed on day 16 post induction to osteogenesis.

Gene expression of the cellular senescence effectors, cyclin-dependent kinases inhibitors p16 (Cdkn2a), p21(Cdkn1a) and p53 was significantly higher on HG compared to NG or MAN on day 21. A significantly higher percentage of senescence-associated-galactosidase (β-gal+) cells and p21 protein level were observed on HG compared to NG or MAN. HMGB1, a chromatin protein secreted in senescence due to changes in the nuclear scaffold, was markedly increased in culture media on HG, accompanied by an increase in gene expression of ager coding for RAGE for which HMGB1 is a ligand. Proteomics analysis demonstrated differential proteomic response to HG. Pathway analysis of DEPs on HG vs. NG showed significant enrichment for the senescence pathway with positive activation (Z=1.213; p=1.11E-05). Collectively, this data suggests that sustained hyperglycemia triggers senescence in IDG-SW3 osteocyte-like cells. The effects of senolytic compounds that clear senescent cels need to be investigated in vitro and in vivo.

286

Chronic Intermittent Hypoxia Induces a KLF5-Dependent Shift toward Lipid Oxidation and Glucose Intolerance

Eden Engal[1,2], Hadas Masury-David[2], Naama Lopiansky[1,2], Shirel Fradkov[1,2], Liran Brodsky[1,2], Saja Baraghithy[1], Joseph Tam[1], Xue Sun[3], Oren Ram[3], Asaf Marco[4], Rinat Abramovitch[1,2], Alex Gileles-Hillel[1,5]

[1]*Faculty of Medicine, Hebrew University of Jerusalem*

[2]*The Wohl Institute for Translational Medicine, Hadassah Medical Center*

[3]*Silberman Institute of Life Sciences, Hebrew University of Jerusalem*

[4]*Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem*

[5]*The Wohl Institute for Translational Medicine; Department of Pediatrics, Hadassah Medical Center*

INTRODUCTION: Obstructive sleep apnea (OSA) is a prevalent condition that exposes tissues to chronic intermittent hypoxia (IH) and is associated with adverse metabolic effects. While OSA is strongly linked to insulin resistance and type 2 diabetes, the mechanisms by which IH disrupts metabolic homeostasis remain poorly defined. In contrast, sustained hypoxia (SH), as experienced at high altitude, is associated with improved glucose regulation. Here, we contrast IH with adaptive SH in mice and adipocytes and study their divergent metabolic programs in a multi-omics approach.

METHODS: Male C57BL/6J mice were exposed for ten weeks to room air (RA), IH, or SH. Whole-body metabolism, glucose tolerance, and tissue-specific insulin signaling were assessed. Brown adipose tissue (BAT) underwent integrated multi-omics profiling, including bulk RNA-seq and bisulfite sequencing for DNA methylation. 3T3-L1 adipocytes were exposed in vitro to matched IH and SH paradigms and profiled by single-cell RNA-seq. Available transcriptomic and methylation data from patients with OSA were reanalyzed to identify conserved and clinically relevant regulatory signatures. Transcription factor motif enrichment was performed across all datasets. A selective KLF5 inhibitor was administered in vivo and in vitro to test the reversibility of IH-induced metabolic dysfunction.

RESULTS: IH and SH produced opposing systemic metabolic phenotypes. IH induced glucose intolerance, preferential lipid oxidation, and impaired insulin signaling in BAT, whereas SH improved glucose excursion and favored carbohydrate oxidation. Transcriptomic profiling revealed that IH activated a diabetes-like program enriched for fatty acid metabolism, while SH upregulated glycolysis and canonical hypoxia pathways. IH and SH also drove distinct alternative splicing landscapes, with IH-specific splicing events enriched in metabolic and insulin-responsive genes. DNA methylation patterns further distinguished IH from SH, particularly at loci regulating lipid metabolism and nutrient sensing. OSA patient data analysis revealed similar transcriptional and splicing patterns. Cross-tissue and cross-species transcription factor motif enrichment analyses identified Krüppel-like factor 5 (KLF5) as a conserved driver of the IH maladaptive state, with KLF5 motifs enriched in IH-responsive genes in BAT, liver, adipocytes, and OSA patient samples. Consistently, KLF5 expression and nuclear localization were increased in IH in vivo and in vitro. Pharmacological inhibition of KLF5 reversed IH-induced transcriptional programs and restored insulin-stimulated AKT signaling.

CONCLUSIONS: Chronic IH induces a KLF5-dependent shift toward lipid oxidation and insulin resistance, whereas SH promotes a metabolically favorable state. KLF5 emerges as a reversible regulatory node linking IH to impaired glucose homeostasis, offering a potential therapeutic target for OSA-associated metabolic dysfunction.

287

Low maternal estriol: early indicator of life-threatening adrenal insufficiency

Keren Cohen[1], Naomi Weintrob[2], Amir Peleg[3,4], Lena Sagi Dain[3,4], Ilana Koren[1,4]
[1]*Pediatric Endocrinology Unit, Lady Davis Carmel Medical Center and Clalit Health Services, Haifa, Israel*
[2]*The Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana Dwek Children Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Isreal*
[3]*Genetic Institute, Lady Davis Carmel Medical Center and Clalit Health Services, Haifa, Israel*
[4]*. Ruth and Bruch Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*

Background

Estriol is measured as part of the maternal triple-marker screen for Down syndrome and open neural tube defects. Isolated low estriol levels are associated with impaired uteroplacental perfusion, fetal growth restriction, oligohydramnios, and increased fetal demise risk. Low estriol also serves as a marker of X-linked ichthyosis, placental sulfatase deficiency, aromatase deficiency, and Smith–Lemli–Opitz syndrome (SLOS). Additionally, it may indicate impaired fetal adrenal steroidogenesis due to primary or secondary congenital adrenal insufficiency. delayed recognition of these conditions can lead to adrenal crisis and infant mortality.

Objective

To describe a series of infants with isolated low estriol levels on the maternal triple-marker screen.

Methods

We retrospectively reviewed five cases of infants in whom isolated low estriol levels were identified on the maternal triple-marker screen. Prenatal records, genetic evaluations, neonatal clinical courses, and endocrine workups were analyzed.

Results

Among five cases, two diagnoses—X-linked ichthyosis and Smith–Lemli–Opitz syndrome—were identified prenatally following detection of low estriol levels, in accordance with standard genetic evaluation. Three additional cases of adrenal insufficiency were diagnosed only postnatally, including adrenal hypoplasia congenital (AHC), 17-hydroxylase/17,20-lyase deficiency, and ACTH deficiency as part of multiple pituitary hormone deficiency due to posterior ectopic hypophysis. Retrospective review of prenatal screening demonstrated isolated low estriol levels in all three cases, which had not prompted further evaluation at or immediately after delivery.

All three cases presented with neonatal hypoglycemia; the case with adrenal hypoplasia congenita additionally had severe hyponatremia and hyperkalemia. All three demonstrated low cortisol responses to intravenous Synacthen testing and were treated with hydrocortisone, with 9-α-fludrocortisone added when indicated.

Conclusions

Our case series highlights the importance of recognizing low estriol on the maternal triple-marker screen as a potential early indicator of impaired fetal adrenal function. Accordingly, prompt postnatal evaluation of the hypothalamic–pituitary–adrenal axis should be undertaken in infants born after unexplained maternal low estriol levels.

288

Decoding Cellular Heterogeneity With Single-Cell and Single-Nucleus Transcriptomics in Endocrinology Research

Oleg Zilber[1], Alon Zemer[1], Yulia Haim[1], Habib Muallem[1], Uri Yoel[2], Assaf Rudich[1]
[1]*Biochemistry, Ben Gurion University*
[2]*Endocrinology, Soroka University Medical Center*

The endocrine system relies on intricate communication between highly specialized cell types to maintain homeostasis. Yet, many traditional research methods mask the signals of rare, transitional, or highly localized cell populations that contribute to disease, or fail to provide a deep characterization of cellular diversity. Single-cell and single-nucleus RNA sequencing are leading single-cell omics technologies, offering higher resolution of the cell types involved in physiology and in pathogenic states, including in endocrinology.

This presentation is designed as a "guided tour" through the methodological basis and the architecture of a single-cell study in an attempt to demystify the workflow—from the strategic choice between profiling whole cells versus isolated nuclei to the critical interpretation of standard visualizations of results. These will be illustrated by examples from studies by our group (murine hypothalamus; human adipose tissue) and others (gastric epithelial plasticity), highlighting three key analytical layers:

Cluster & Cell Annotation: Moving beyond biased marker selection to define cell identity through unbiased clustering. Illustrated by the establishment of the human white adipose tissue atlas to identify "non-classical" adipocyte subpopulations.
Cell Sub-populations with Unique Roles: Investigate how specific cell subsets may drive disease states based on their proposed distinct presumed functions. Exemplified by the study of the molecular drivers of central aging in the hypothalamus, employing pathway enrichment analysis to infer the presumed inflammatory microglial subsets characterised by aggravated and persistent gene patterns.
Trajectory Analysis & Cell-Cell Communication: Moving from static cell annotation to dynamic states reconstruction. Demonstrated by utilizing pseudotime trajectory inference to reconstruct the lineage reprogramming of isthmus progenitors following bariatric surgery, and applying ligand-receptor interaction mapping to decode the intercellular crosstalk driving adaptive shifts.

We will conclude by discussing next-step technologies such as spatial transcriptomics, and how they can allow the reconstruction of tissue zonation, and how they will enable addressing more questions pertinent to advancing endocrine research and precision medicine.

Asthma and stress fractures in combat soldiers: A nationwide military database study

Bar Lossos[1,2], Harel Gershgoren[1,2], Idan Levi[1], Maayan Shaked[1], Amit Rimon[1,2], Hadasa Sharshevsky[1], Tomer Talmy[1], Meir Schechter[1,3]

[1]*Medical Data Research Institute, Israel Defense Forces Medical Corps, Tel HaShomer, Ramat Gan, Israel*

[2]*Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*

[3]*Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel*

Background

Older adults with chronic corticosteroid-treated asthma have a higher risk of fractures, potentially attributable to the corticosteroids exposure and systemic inflammation. It is less clear whether young adults with mild asthma treated less rigorously with inhaled corticosteroids have compromised bone health. Stress fractures (SFs) are common in military training and arise due to an imbalance between microdamage accumulation and the bone's ability to remodel and repair. Unique to the Israeli Defense Forces (IDF) is the integration of individuals with mild asthma into selected active combat roles. This setting provides a unique opportunity to assess the association between mild asthma and SF risk as a marker of bone health in young adults.

Methods

In a retrospective cohort study using the IDF electronic medical records, we included active-duty combat soldiers aged 18-25 years recruited between 2010-2025. We only included those recruited to combat roles of lower intensity such as the armored corps, artillery, and border defense, where young adults with mild asthma are eligible to serve. The exposure included three arms: mild active asthma, asthma in remission, or no asthma. We used univariate and multivariable-adjusted Cox proportional hazards regression models to assess the risk of stress fractures, identified using ICD-10 codes. The model was adjusted for socioeconomic status, body mass index and cognitive function. Analyses were performed separately in men and women.

Results

There were overall 81,350 combat soldiers (23,261 [28.6%] women). Among men, 2,092 (3.6%), 1,095 (1.9%), and 54,902 (94.5%) had mild active asthma, remitted asthma, and no asthma respectively. The respective number of men experiencing SF were 134 (6.4%), 67 (6.1%), and 3,065 (5.6%). Individuals with mild and remitted asthma had an adjusted hazard ratio for SF of 1.088 [95% CI 0.914-1.294] and 1.101 [0.864-1.403], respectively, compared with those without asthma. Among women, 180 (0.7%), 181 (0.7%), and 22,900 (98.4%) had mild active asthma, asthma at remission, and no asthma respectively. The respective number of women experiencing SF were 30 (16.6%), 20 (11%), and 2,469 (10.8%). The estimated adjusted HR for the risk of stress fracture was 1.653 [95% CI 1.153-2.369] for women with mild asthma and 1.09 [95% CI 0.702-1.693] for those with remitted asthma compared with those without asthma.

Conclusion

Mild active asthma was associated with an increased risk of stress fractures in young women but not in men. Limited by a relatively low number of events, these results highlight the importance of further investigation

291

Association Between Adherence to Inpatient Diabetes Care Guidelines and Hospitalization Complications: A Multicenter Real-World Study

Shahar Oded[1], Yuval Shahar[1], Erez Shalom[1], Amir Bashkin[2,3], Leonard Saig[4,5], Dror Cantrell[6], Irit Wirsansky[7], Muhamad Badarne[2,8], Irena Barash[9], Avivit Cahn[10,11], Irit Hochberg[4,7], [1]*Medical Informatics Research Center, Ben Gurion University, Be'er Sheva, Israel*, [2]*Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel*
[3]*Endocrinology and Diabetes unit, Galilee Medical Center, Naharia, Israel*
[4]*Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel*, [5]*Endocrinology Institute, Bnai Zion Medical Center, Haifa, Israel*
[6]*Internal Medicine Department C, Shamir Medical Center, Be'er Ya'akov, Israel*
[7]*Endocrinology Unit, Hillel Yaffe Medical Center, Hadera, Israel*
[8]*Endocrinology and Diabetes Service, Tzafon Medical Center, Ramat Poriya, Israel*
[9]*Internal Medicine C, Barzilai Medical Center, Ashkelon, Israel*
[10]*Internal Medicine Department A, Hadassah Ein Kerem, Jerusalem, Israel*
[11]*Faculty of Medicine, Hadassah Hebrew University Hospital, Jerusalem, Israel*

Background Diabetes and inpatient hyperglycemia affect over one-third of hospitalized adults and are associated with prolonged length of stay and increased risk of complications. Despite established guidelines, real-world adherence to inpatient insulin-based diabetes management remains variable, and its clinical impact is incompletely characterized. This study evaluates the effect of national guidelines, staff training, and formal quality indicators on adherence to inpatient diabetes care and associated clinical outcomes. In addition, we describe ongoing work leveraging longitudinal adherence and glycemic data to inform predictive models of hospital-acquired complications.

Methods We conducted a multicenter observational study using the Israeli Ministry of Health Kineret Dataset, including adult inpatients with diabetes or recurrent glucose measurements 180 mg/dL across six general hospitals. Adherence to inpatient diabetes management guidelines was assessed using a structured, time-aware clinical quality framework capturing key processes of care, including glucose monitoring frequency, insulin administration, de-escalation following hypoglycemia, and suspension of oral glucose-lowering agents. Outcomes included length of stay, hospital-acquired (≥48 hours after admission) hypoglycemia, nosocomial infections, acute kidney injury, cardiovascular events, and mortality.

Machine-learning methods, including bootstrapped elastic-net multivariable models, were used for feature selection and to quantify the association between guideline adherence scores and hospital-acquired complications.

Results The cohort included 17,314 adult patients admitted between July 2022 and July 2024; 55% had a documented diagnosis of diabetes, while 45% had recurrent or severe hyperglycemia without a prior diabetes diagnosis. Among patients with diabetes, 52% maintained target glucose levels (70–180 mg/dL) early during hospitalization. In contrast, 74% of patients without a diabetes diagnosis experienced at least one extreme glucose value (250 or 54 mg/dL) within 48 hours of admission.

Following national guideline implementation, the greatest improvements in adherence were observed in discontinuation of medications with high hypoglycemia risk, insulin dose reduction after hypoglycemia, and repeat glucose monitoring. SGLT2 inhibitors were consistently suspended during hospitalization, high-risk hypoglycemic agents were withheld after hypoglycemia in over 80% of cases, and inpatient metformin use declined. Higher adherence was associated with lower in-hospital or near-discharge mortality. Feature selection analyses demonstrated that guideline adherence accounted for up to 40% of the predictive contribution for hospital-acquired complications, with insulin protocol adherence showing the strongest associations with hypo- and hyperglycemic events.

Conclusions Improved adherence to inpatient diabetes management guidelines is associated with reduced hospital-acquired complications, providing large-scale real-world evidence that systematic, guideline-based care enhances patient safety in general hospital settings.

292

Clinical utility of the SARC-F questionnaire for assessing sarcopenia in community-dwelling older adults with diabetes and obesity

Sharon Barak[1], Roy Eldor[2], Roy Brown[2], Orly Barak[2], Elena Izkhakov[2], Yona Greenman[2], Carla M Prado[3], M. Cristina Gonzalez[4], **Assaf Buch**[5]

[1]*Ariel University*

[2]*Tel Aviv Sourasky Medical Center*

[3]*Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada*

[4]*Federal University of Pelotas, Pelotas, RS, BR*

[5]*Ariel University ; Tel Aviv Sourasky Medical Center*

Background and aims: Sarcopenic obesity is increasingly recognized among older adults with type 2 diabetes mellitus (T2DM). Despite the clinical importance of early identification, few validated tools exist to screen for sarcopenia in individuals with obesity within this high-risk group. The Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls questionnaire (SARC-F) is a widely used sarcopenia screening tool. However, its diagnostic validity in populations with both obesity and T2DM remains unclear. The present study aimed to evaluate the reliability (internal consistency) and validity (construct and discriminative) of the SARC-F in detecting sarcopenia among older adults with obesity and T2DM. Materials and Methods: This cross-sectional study included community-dwelling older adults (≥65y) with T2DM and obesity (based on body mass index, waist circumference, or fat percentage) who completed the SARC-F questionnaire. Sarcopenic obesity was diagnosed using the Sarcopenic Obesity Global Leadership Initiative (SOGLI) consensus criteria using bioelectrical impedance analysis, maximal handgrip strength, lower extremity strength, or lower extremity muscular endurance. The prevalence of sarcopenic obesity was calculated, and correlations were used to analyze the associations between continuous SARC-F scores and clinical as well as demographic variables. Discriminative validity was examined with receiver operating characteristic (ROC) analysis. Results. One hundred older adults with T2DM and obesity (mean age 70.4 ± 4.6 years; 60% women) were included; 72% presented with sarcopenic obesity. The SARC-F showed acceptable reliability (ordinal alpha = 0.72). ROC analysis showed that the SARC-F score moderately discriminated poor performance when the 30 Seconds Sit-to-Stand Test (highest AUC) was used as reference (AUC = 0.76; negative predictive value = 68%), and the lowest when handgrip strength was used (AUC = 0.62 without adjusting to weight and 0.58 with weight adjustment; negative predictive value = 37% and 41%, respectively). Conclusion: The SARC-F showed moderate validity but limited sensitivity and negative predictive value, especially if the handgrip strength is used, suggesting it may have limited utility as a standalone tool for sarcopenic screening in older adults with T2DM and obesity.

293

Impact of standing desks on physiological and psychological outcomes in sedentary office workers

Assaf Buch[1,2], Ofer Kis[2], Lani Ofri[1], Odelyah Saad[1], Liat Kulik[3], Roy Eldor[2]
[1]*Ariel University*
[2]*Tel Aviv Sourasky Medical Center*
[3]*Bar Ilan University*

Background & Aims: Sedentary work environments are associated with metabolic risks. This pilot study investigated the physiological and psychological effects of introducing standing desks in a sedentary office setting.

Methods: A one-month interventional study was conducted with 10 healthy office workers (7 women, age 36.5 ± 1.86 years). Participants were provided adjustable standing desks and instructed to stand at will. Assessments included calorie expenditure, steps/24 hours, distance traveled/24 hours, heart rate, continuous glucose monitoring, carbohydrate utilization
(assessed by morning, fasting exhaled CO2 measurements), body composition analysis, comprehensive physiological measurements, participant/control group, and supervisor work satisfaction and assessment questionnaires. Ethics Approval: Tel-Aviv Sourasky Medical Center IRB (0076-21-TLV)

Results: During total working days (n=18), the overall standing time across all participants during the intervention was 235 ± 119 (SD) minutes per workday (≈3 hours and 55 minutes). Participants demonstrated a slight increase in daily physical activity with 8.5% more steps/day (7926 ± 2658 vs. 7304 ± 2752, p=0.19) and 10.9% greater distance (6582 ± 2296 vs. 5936 ± 2334, p= 0.14) while maintaining similar caloric expenditure (2087 ± 413 vs. 2098 ± 407, p=0.41) and exhibiting a reduced mean 24-hour heart rate (73 ± 3 vs. 76 ± 2 bpm, p= 0.02). Improvement was noticed in the 30-second chair stand test (27.6 ± 2.6 vs. 20.6 ± 5.4 repetitions, p=0.006) with no change in maximum leg extension strength. Body weight increased from 65.6 to 68.4 kg (p0.001), primarily due to increased body fat percentage (+1.76%; p=0.049) with no change in muscle mass. Total caloric consumption was slightly higher (1780±220 kcal vs. 2375±222 kcal, p=0.13) with a trend towards increased consumption of all macronutrients. Fasting carbohydrate utilization was unchanged (Lumen score 4.51 ± 0.28 vs 4.54 ±0.25, p=0.20) while 24-hour glucose increased from 88.5 to 93 mg/dL (p=0.013). Workplace assessment of well-being suggested an overall improvement in workplace satisfaction, higher energy levels, and a reduction in work-related stress (compared to matching controls).

Conclusion: Standing desks significantly improved workplace wellbeing while yielding mixed physiological outcomes. Despite increased standing time, participants showed minimal changes in activity metrics and unexpectedly gained weight, driven by increased body fat and higher 24-hour glucose levels post-intervention. The most consistent benefits were psychological rather than metabolic, suggesting that standing desks primarily enhance perceived well-being rather than directly improving metabolic parameters in healthy office workers.

294

Optimizing Patient Selection for Adrenal Vein Sampling in Primary Hyperaldosteronism

Meir Frankel[1], Anthony Verstandig[2], Gavriel Lichewitz[1], Noa Sylvetzky[1], Gabriel Munter[1]
[1]*Endocrinology unit, Shaare Zedek Medical Center, affiliated to Faculty of Medicine, Hebrew University, Jerusalem, Israel*
[2]*Interventional radiology unit, Shaare Zedek Medical Center, affiliated to Faculty of Medicine, Hebrew University, Jerusalem, Israel*

Background

Primary hyperaldosteronism (PA) is caused by excessive aldosterone production from one or both adrenal glands. Diagnostic evaluation includes biochemical testing, imaging, and in most patients requires adrenal vein sampling (AVS) to differentiate unilateral disease, which may benefit from surgical treatment, from bilateral disease, which is managed medically.

According to 2025 Endocrine Society guidelines, screening for PA is recommended in all patients with hypertension, a strategy that is expected to increase PA detection. Following biochemical confirmation, AVS is generally recommended for patients with a moderate/high likelihood of unilateral disease, while those with a low probability are managed with medical therapy as first-line treatment. Identifying clinical predictors of unilateral aldosterone secretion may therefore optimize patient selection for AVS.

Methods

We retrospectively analyzed all patients with confirmed PA who underwent AVS at Shaare Zedek Medical Center during 2019-2025, with successful determination of unilateral or bilateral aldosterone secretion according to accepted criteria. Baseline demographic, clinical, and imaging variables were evaluated using statistical analyses to identify predictors of unilateral disease and to develop a predictive model for AVS outcomes.

Results

During the study period, 85 patients with PA underwent AVS with definitive classification of aldosterone secretion as unilateral or bilateral. Unilateral aldosterone secretion was identified in 55 patients (65%), while 30 (35%) had bilateral disease.

In univariable analysis, hypokalemia was strongly associated with unilateral aldosterone secretion (odds ratio [OR] =16.7), as was a lowest recorded serum potassium level 3.3 mEq/L (OR=8.3). An aldosterone-to-renin ratio (ARR) 10 was also significantly associated with unilateral disease (OR=4.5). Chronic kidney disease was significantly associated with bilateral aldosterone secretion (OR=0.3). Baseline low renin levels demonstrated a borderline association with unilateral disease (OR=1.9). Age, Gender, age at hypertension diagnosis, serum aldosterone level and adrenal mass (uni or bilateral) in imaging were not significantly associated with AVS results.

In multivariable logistic regression analysis, a lowest serum potassium level3.3 mEq/L and ARR10 remained independently and strongly associated with unilateral aldosterone secretion. A predictive model based on these variables achieved an overall accuracy of approximately 80% in predicting AVS outcomes.

Conclusions

Patients with PA and unilateral aldosterone secretion exhibit distinct baseline clinical and biochemical characteristics compared to patients with bilateral disease. These findings, together with the predictive model developed in this study, may assist clinicians in determining whether to initiate medical therapy as first-line treatment or to proceed with AVS to evaluate candidacy for surgical management of unilateral disease.

295

Body Mass Index and Discharge Destination After Major Elective Orthopedic Surgery: A Retrospective Cohort Study

Dana Kagansky[1,2], Ofir Vinograd[1,3], Michal Bitan[4], Hitam Hagog Natour[5], Orna Tal[1]

[1]*Shamir Medical Center (Assaf Harofeh), Zerifin, Israel*

[2]*Institute of Endocrinology, Diabetes and Metabolism, Assaf Harofeh Medical Center, Zerifin, Israel, affiliated to the Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

[3]*Department of Orthopaedic Surgery, Shamir Medical Center, Zerifin, Israel, affiliated to the Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

[4]*School of Computer Science, The College of Management Academic Studies, Rishon LeZion, Israel*

[5]*Institute of Endocrinology, Diabetes and Metabolism, Meir Medical Center, Kfar Saba, Israel*

Background: Discharge destination after elective major orthopedic surgery influences health system capacity, costs, and post-acute care utilization. Although body mass index (BMI) is routinely documented in preoperative risk assessment, it is not a formal criterion for discharge planning, and evidence regarding its independent association with discharge destination remains limited. This study examined the association between BMI and discharge destination following major orthopedic surgery.

Methods: We conducted a retrospective cohort study of adult patients undergoing major elective orthopedic surgery at a tertiary medical center between 2015 and 2025. Eligible procedures included spine surgery, total knee replacement, and total hip replacement. BMI was calculated at admission and analyzed both categorically and continuously. The primary outcome was discharge destination, classified as home or institutional rehabilitation. Multivariable logistic regression was used to evaluate the association between BMI and discharge to institutional rehabilitation, adjusting for age, sex, type of surgical procedure, and length of hospital stay.

Results: The final cohort included 3,617 patients (mean age 65 years; 55% female), of whom 22% were discharged to institutional rehabilitation. Discharge to rehabilitation increased across BMI categories, from 20% among patients with BMI 25 kg/m² to 25% among patients with BMI 30 kg/m² (p0.001). In multivariable analysis, higher BMI was independently associated with discharge to rehabilitation (OR 1.03 per kg/m²; 95% CI 1.01–1.04), after adjustment for age, sex, surgical procedure, and length of hospital stay.

Conclusions: Higher BMI was independently associated with discharge to institutional rehabilitation following major elective orthopedic surgery, beyond differences explained by hospitalization duration and procedural factors. These findings suggest that discharge destination represents a consequential and potentially system-influenced outcome, highlighting the need for more standardized, function-based discharge criteria.

296

Real-World Outcomes of Immune Checkpoint Inhibitor Therapy in Differentiated and Anaplastic Thyroid Carcinoma: A Retrospective Case Series

Irit Ayalon-Dangur[1,2], Eyal Robenshtok[1,2], Elena Itzhakov[2,3], Liyona Kampel[2,4], Inbar Finkel[2,5]

[1]*Institute of Endocrinology, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel.*
[2]*Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.*
[3]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.*
[4]*Department of Otolaryngology-Head and Neck and Maxillofacial Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.*
[5]*Oncology Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.*

Introduction: Immune checkpoint inhibitors (ICIs), that target regulatory pathways such as PD-1/PD-L1 and CTLA-4, have revolutionized the treatment landscape for several solid tumors, however their application in thyroid cancer is an area of growing interest. Studies have demonstrated that ICIs, either as monotherapy or in combination with TKIs or BRAF inhibitors, can induce meaningful responses in anaplastic thyroid cancer (ATC), but there is limited data on their efficacy in differentiated thyroid cancer (DTC). The aim of the current study was to evaluate real-world outcomes of ICI therapy in patients with metastatic or radioactive iodine ablation (RAI) resistant DTC and ATC.

Methods: A retrospective case series included patients who received ICI treatment with or without biologic therapy, for differentiated or anaplastic thyroid cancer with systemic or unresected disease, between August 2018 and August 2025 in two tertiary centers, Tel Aviv Sourasky Medical Center, and Rabin Medical Center. All patients were treated by the same oncologist. Demographic, clinical, and treatment data were collected from the EMR. Patient records were analyzed to evaluate the outcomes of best overall response (by RECIST 1.1), duration of response, progression-free and overall survival, as well as adverse events. Tumor measurements were assessed radiographically with PET-CT at baseline and every 3-4 months. The study protocol was approved by the TLVMC Institutional Review Board.

Results: Ten patients included in the study, mean age 69.2 years, 40% females. The thyroid cancer subtype included six ATCs, one mixed papillary and anaplastic, one oncocytic cell carcinoma and one poorly diffrentiated thyroid cancer. Three of the anaplastic tumors were dedifferentiated. Seven patients underwent surgical resection (six total thyroidectomy+neck dissection and one hemithyroidectomy). Six patients received RAI and six patients received external beam badiation therapy to the neck. The ICI agent was Pembrolizumab in seven patients (70%) and Nivolumab in three patients (30%). Five patients received ICI+Lenvatinibe, one patient received ICI as monotherapy, and four patients received more than on treatment line. Overall, six patients (60%) experienced partial response, two patients (20%) experienced stable disease, and for two patients (20%) the best response wasn’t determind. Three grade 4 and three grade 2 adverse events were reported. Five patients died during the follow-up, one from T-cell lymphoma and the other from thyroid cancer.

Conclusion: This study demonstrates responsiveness to ICI therapy, predominantly in combination with biologic agents, in a subgroup of patients with differentiated or anaplastic thyroid cancer who have systemic disease or unresectable tumors.

297

Sustained Low-Normal TSH and Risk of Atrial Fibrillation and Vertebral or Hip Fractures

Said Darawshi[1], Ruba Gadban[2], **Afif Nakhleh**[3,4]
[1]*Clalit Healthcare Services, Northern District, Nazareth, Israel*
[2]*. Department of Internal Medicine D, Rambam Health Care Campus, Haifa, Israel*
[3]*Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus, Haifa, Israel*
[4]*Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel*

Background: Subclinical hyperthyroidism is a well-established risk factor for atrial fibrillation and osteoporotic fractures. However, it remains unclear whether this risk extends to low-normal thyroid-stimulating hormone (TSH) levels. We evaluated the association between sustained low-normal TSH levels and the incidence of atrial fibrillation and vertebral or hip fractures.

Methods: We conducted a retrospective cohort study using data from Clalit Healthcare Services (CHS), Israel, from January 1, 2002, through June 30, 2025. The study included 674,288 adults aged ≥50 years who had two consecutive TSH tests at least 6 months apart, with both results falling within the same predefined range (0.4, 0.4 to 1.0, or 1.0–2.5 mIU/L) within a two-year period. The index date was defined as the date of the second TSH result. Inclusion was restricted to individuals with continuous CHS coverage throughout follow-up period. Individuals were excluded if they had free T4 or free T3 levels above the upper limit of normal; a history of anti-thyroid medication or levothyroxine treatment, radioactive iodine, or thyroid surgery; or a diagnosis of atrial fibrillation, osteoporosis, or vertebral or hip fractures prior to the index date. Follow-up continued until June 30, 2025 or death. The cohort was stratified into three groups: low TSH (0.4 mIU/L; n=8,494), low-normal TSH (0.4 to 1.0 mIU/L; n=107,791), and reference (1.0–2.5 mIU/L; n=558,003). Multivariable Cox proportional hazards regression models were used to estimate the risk of incident atrial fibrillation and first vertebral or hip fracture, adjusted for age and sex.

Results: The mean age of the cohort at the index date was 63.0±10.9 years, and 49% were female. The median follow-up was 12.9 (IQR 6.4–17.9) years. Compared with the reference group (1.0–2.5 mIU/L), the low-normal TSH group (0.4 to 1.0 mIU/L) had an increased risk of incident atrial fibrillation (hazard ratio (HR) 1.05; 95% CI 1.03–1.06) and vertebral or hip fracture (HR 1.12; 95% CI 1.10–1.14). In the low TSH group (0.4 mIU/L), the risk was also elevated for atrial fibrillation (HR 1.16; 95% CI 1.11–1.22) and vertebral or hip fracture (HR 1.13; 95% CI 1.06–1.19).

Conclusion In this large cohort of adults aged ≥50 years, sustained low-normal TSH levels were independently associated with increased risks of atrial fibrillation and vertebral or hip fractures. These findings suggest that the lower end of the TSH reference range may represent a risk state for cardiovascular and skeletal health in older adults.

298

A PILOT STUDY COMPARING THE EFFICACY OF DOSING ULTRA RAPID INSULIN LISPRO IN A MEDTRONIC 780G HYBRID CLOSED LOOP SYSTEM AT MEALTIME OR POSTMEAL

Roy Eldor[1,2], Eugene Merzon[3,4], Miri Margaliot[1], Tamara Kolitz[1], Assaf Buch[1,4]
[1]*Tel Aviv Sourasky Medical Center*
[2]*Tel-Aviv University*
[3]*Leumit HMO, Medical Division*
[4]*Ariel University*

Background and aims - Hybrid closed-loop systems have revolutionized insulin delivery in Type 1 Diabetes Mellitus (T1DM), with the MiniMed 780G (780G) system demonstrating significant improvements in glycemic control. Current protocols recommend premeal bolusing, requiring carbohydrate estimation before consumption. However, approximately 34% of T1DM patients regularly administer meal boluses during or after meals, which has been associated with poorer glycemic outcomes. Ultra rapid insulin lispro (URLi) offers faster absorption kinetics than traditional insulin analogs. This pilot study aims to investigate whether the rapid absorption profile of URLi combined with the autocorrection features of the MiniMed 780G system could enable effective postmeal dosing without affecting parameters of glycemic control.

Methods: Adult patients with T1DM who have been using the 780G with URLi for ≥2 months were included. Before participating in this study, all patients were routinely instructed during clinic visits to administer meal bolus doses before consuming meals. After informed consent, baseline data was collected from the Medtronic Carelink platform and subjects entered a 4-week intervention period, during which they were instructed to administer meal-bolus doses only at the end of meals.

Results- We present here preliminary results from 12 patients (7/56.3% female; age 40.9 ± 16.3 years ; diabetes duration 15.5 ± 11.4 years ; use of the MiniMed 780G with URLi for 16.9 ± 6.8 months; HbA1c - 6.7% ± 1.0; BMI= 25.1 ± 6.0). Smart guard and sensor use were high and similar before and during the intervention (90.1% vs 93.9% and 88.3% vs 91.3% respectively). Comparing baseline/pre-meal bolus dosing to postmeal URLi dosing, we observed no significant differences in time in range (70-180 mg/dL) (70.0 ± 11.9% vs. 71.4 ± 10.8%, p=0.48), time in tight range (70-140 mg/dL) (45.0 ± 11.0 vs. 45.7 ± 11.3, p=0.74), glucose management indicator (GMI) (7.0 ± 0.3 % vs 7.0 ± 0.4%, p=0.29) and glycemic variability (coefficient of variation 33.8 ± 5.2% vs 32.7 ± 4.7%, p=0.41). Total daily insulin dose increased slightly (57.1 ± 36.8 vs 60.2 ± 36.7 units, p=0.03) as did basal insulin delivery (23.5 ±19.0 vs. 26.5 ± 20.6, p=0.005).

Conclusion- Postmeal dosing of URLi in the 780G system provides glycemic control comparable to conventional premeal dosing in patients with T1DM. Combining ultra-rapid insulin with advanced hybrid closed-loop technology may offer greater flexibility in bolus timing without compromising outcomes, particularly benefiting patients who struggle with pre-meal carbohydrate estimation or prefer the convenience of post-meal dosing.

299

Adolescent Body Mass Index and Multimorbidity Before Age 50

Avishai M. Tsur[1,2], Estela Derazne[1,3], Arnon Afek[4], Gabriel Chodick[3], Gilad Twig[5,6]
[1]*Medical Corps, Israel Defense Forces*
[2]*Faculty of Medicine, Department of Military Medicine, Hebrew University of Jerusalem*
[3]*Faculty of Medical and Health Sciences, School of Public Health, Tel Aviv University*
[4]*Dina Recanati School of Medicine, Reichman University*
[5]*The Institute of Endocrinology Diabetes and Metabolism, Sheba Medical Center*
[6]*Department of Preventive Medicine and Epidemiology, School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University*

Introduction
Multimorbidity—the accumulation of multiple chronic conditions—is increasingly observed among younger adults. Identifying early-life risk factors, such as adolescent body mass index (BMI), could help prevent long-term disease burdens.

Objectives
To examine the association between adolescent BMI and the risk of developing multimorbidity—defined as the presence of up to four cardiometabolic or vascular conditions—before age 50.

Methods
This nationwide cohort study included 899,897 Israeli adolescents (aged 16–20) who were examined for military service between 1979 and 2019. Individuals with prior cardiometabolic diagnoses were excluded from the study. BMI was measured at baseline and classified as Low-Normal, High-Normal, Overweight, or Obese. Multimorbidity was defined as the presence of up to four of the following conditions: myocardial infarction, stroke, heart failure, peripheral vascular disease, atrial fibrillation, valvular disease, diabetes, hypertension, chronic kidney disease, or cancer. Follow-up extended to December 31, 2021, age 50, death, or loss to follow-up. Cox proportional-hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for sociodemographic and clinical covariates.

Results
Over a median follow-up of 20.0 years (18.0 million person-years), 108,173 participants developed one or more morbidities. Compared with Low-Normal BMI, fully adjusted HRs for a single morbidity were 1.27 (95% CI, 1.25–1.28) for High-Normal, 1.80 (1.76–1.84) for Overweight, and 2.67 (2.59–2.75) for Obesity. For double morbidity, HRs were 1.73 (1.66–1.80), 3.58 (3.41–3.76), and 6.09 (5.73–6.46); for triple morbidity, 2.34 (2.13–2.58), 6.04 (5.41–6.74), and 11.64 (10.29–13.17); and for quadruple morbidity, 2.58 (2.00–3.32), 6.98 (5.24–9.31), and 15.73 (11.60–21.34), respectively. These associations were consistent across sex, health status, and time periods. Risk gradients were steeper with each additional morbidity, and the onset occurred earlier in individuals with higher adolescent BMI.

Conclusion
Higher adolescent BMI, including high-normal values, is strongly associated with earlier and more severe multimorbidity. This graded risk pattern highlights the importance of adolescent weight control as a strategic focus in chronic disease prevention.

300

Teenage Obesity and Incident Cardiovascular Disease in Young Adulthood

Avishai M. Tsur[1,2], Estela Derazne[3], Arnon Afek[4], Gabriel Chodick[3], Gilad Twig[5,6]
[1]*Medical Corps, Israel Defense Forces*
[2]*Faculty of Medicine, Department of Military Medicine, Hebrew University of Jerusalem*
[3]*School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University*
[4]*Dina Recanati School of Medicine, Reichman University*
[5]*The Institute of Endocrinology Diabetes and Metabolism, Sheba Medical Center*
[6]*Department of Preventive Medicine and Epidemiology, School of Public Health, Faculty of Medical and Health Sciences, Tel Aviv University*

Introduction
The global burden of cardiovascular disease (CVD) in young adults is increasing. Elevated body mass index (BMI) in adolescence may contribute to this trend, but large-scale longitudinal data quantifying its association with early CVD events are limited.

Objectives
To evaluate the association between adolescent BMI and the risk of incident CVD events by age 50.

Methods
In this nationwide cohort study, 900,573 Israeli adolescents (aged 16–20) evaluated for military service between 1979 and 2019 were followed through December 31, 2021, death, loss to follow-up, or age 50. Individuals with prior CVD or chronic metabolic conditions were excluded. BMI was measured at baseline and categorized into Low-Normal, High-Normal, Overweight, and Obese. Incident CVD (ischemic heart disease and cerebrovascular events) was ascertained from electronic health records. Cox proportional-hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for sociodemographic and clinical variables. Penalized spline models explored exposure dose-response relationships.

Results
During a mean follow-up of 20.0 years (18 million person-years), 6,242 CVD events occurred. Crude incidence rates increased across BMI groups: 3.0, 3.6, 4.8, and 5.8 per 10,000 person-years for Low-Normal, High-Normal, Overweight, and Obesity, respectively. Compared with Low-Normal BMI, fully adjusted HRs for CVD were 1.36 (95% CI, 1.28–1.44) for High-Normal, 1.94 (1.78–2.11) for Overweight, and 2.38 (2.12–2.66) for Obesity. These associations were consistent across sexes and socioeconomic strata. Spline models revealed a continuous, approximately log-linear increase in risk across the BMI spectrum with no apparent threshold. Associations persisted after adjustment for comorbidities and exclusion of individuals with baseline impairments.

Conclusion
Higher adolescent BMI, including values in the high-normal range, is associated with significantly increased CVD risk before age 50. These findings suggest that early BMI trajectories are critical to long-term cardiovascular health and support prioritizing adolescent weight management in preventive strategies.

301

Serum vitamin D levels and functional recovery after hip fracture rehabilitation: a national quality registry-based cohort study

Limor Friedensohn[1,2], Olga Bronshtein[1], Nethanel Goldschmidt[1]
[1]*Quality and Patient Safety Division, Israeli Ministry of Health*
[2]*Division of Endocrinology, Metabolism and Diabetes, Sheba Medical Center*

Background:
Lower serum levels of 25-hydroxyvitamin D (25(OH)D) are associated with poorer functional status and reduced recovery after hip fracture in adults aged ≥65 years, although associations with rehabilitation length of stay (LOS) are inconsistent. Most studies focus on deficiency versus sufficiency, with limited data on outcomes across the full spectrum of vitamin D levels.

Objective:
To evaluate the association between acute-phase serum 25(OH)D levels and functional status and recovery during rehabilitation in a national cohort of older adults following surgically treated hip fracture.

Methods:
This retrospective cohort study used data from the Israeli National Program for Quality Indicators. All patients aged ≥65 years admitted to Israeli general hospitals in 2024 with hip fracture, who underwent surgery and had serum 25(OH)D measured during acute admission, were included. Vitamin D levels (nmol/L) were classified as 25, 25-49.9, 50-74.9, 75-125, and 125. Functional outcomes were assessed using the Functional Independence Measure (FIM) at admission to and discharge from rehabilitation. Functional improvement was defined as ΔFIM.

Results:
The cohort included 1,469 patients, median age 84 years (IQR 77-89), 69% females. Mean FIM score at admission was 61±15 points and mean functional improvement (ΔFIM) was 24±14 points. Median rehabilitation LOS was 32 days. Advancing age and impaired cognitive screening status were associated with lower admission FIM scores and smaller functional gains, while LOS remained relatively stable.

Across vitamin D categories, admission FIM scores varied modestly, while functional recovery demonstrated a non-linear pattern. Patients with intermediate serum 25(OH)D levels (50-74 and 75-125 nmol/L) achieved the highest admission FIM scores and greatest functional gains (mean FIM 64±15 for younger patients and 56±13 for older patients; ΔFIM 24-26 points). In contrast, patients with 25 nmol/L (mean FIM 59.6±13 for younger and 52.5±12 for older patients; ΔFIM 21 points) and those with 125 nmol/L (mean FIM 62±15 for younger and 55±9 for older patients; ΔFIM 18 points) showed lower improvement. No consistent association was observed between serum vitamin D levels and LOS.

Conclusions:
In this national quality registry-based cohort, serum vitamin D levels were associated with functional recovery after hip fracture rehabilitation in a non-linear manner. Intermediate vitamin D levels were associated with greater functional gains, supporting the concept of an optimal therapeutic range rather than a linear dose-response relationship, with potential implications for precision endocrine management in post-fracture recovery.

302

The association between CGM derived glycemic control measures at different gestational periods among women with pregestational T1D and the risk of LGA.

Yael Keler[1], Tali Cukierman-Yaffe[1]
Institute of Endocrinology and Diabetes, Sheba Medical Center

Introduction:
Type 1 diabetes (T1D) is associated with an increased risk of perinatal and neonatal complications. Large for gestational age (LGA) is a frequent neonatal complication and is strongly related to maternal glycemic control during pregnancy. Previous studies have shown that poor glycemic control in late pregnancy is associated with an increased risk of LGA. However, the gestational period during which glycemic control is most critical for reducing LGA risk remains uncertain. In addition, few studies have used continuous glucose monitoring (CGM) data to assess the relationship between glycemic control at different stages of pregnancy and LGA or other neonatal outcomes.

Aim: This study aimed to examine the association between CGM derived glycemic control measures at different gestational periods among women with pregestational T1D and the risk of LGA.

Methods:
This study included 110 singleton pregnancies among 76 women with pregestational T1D who were monitored at the High-Risk Pregnancy Clinic and delivered at Sheba Medical Center from May 5, 2011 to April 11, 2022. The sample included patients with available CGM data during pregnancy and documented neonatal birth weight. Demographic and clinical data, as well as neonatal birth weight, were obtained from medical records. CGM data were downloaded from patient sensors at each clinic visit. The raw data was extracted and time in range (TIR; 63-140 mg/dL) and time above range (TAR; 140 mg/dL), as well glucose variability (standard deviation) were calculated for each trimester. Data was statistically analyzed using logistic regression, with neonatal LGA the dependent variable and glucose indices the independent variable.

Results:
Among singleton pregnancies in women with pregestational T1D, higher TAR during the first trimester (30% vs. 24%, p=0.021) was associated with the risk of LGA. During the second trimester, lower TIR (61% vs. 67%, p=0.003) and higher TAR (30% vs. 24%, p=0.004), as well as higher glucose variability (SD: 49.29 vs. 42.63, p=0.001) were associated with the risk of LGA.

Discussion:
In this cohort of singleton pregnancies in women with pregestational T1D, CGM derived glycemic control measures during the first and second trimesters were associated with the risk of LGA, whereas third trimester glycemia was not. These findings suggest that maternal glucose exposure in early and mid-gestation may be important for fetal growth and birth weight. The relatively small sample size may limit the generalizability of these results. Future multicenter studies with larger cohorts are needed.

303

Adrenocortical Carcinoma (ACC) Presenting With Severe Mineralocorticoid Excess and Partial Adrenal Insufficiency: A Possible DOC-Producing Tumor

Tal Netser[1,2], Rabia Hamadi[1,2], Ido Wolf[2,3], Yona Greenman[1,2], Ester Osher[1,2]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center*
[2]*Gray Faculty of Medical and Health Sciences, Tel-Aviv University*
[3]*Department of Oncology, Tel-Aviv Sourasky Medical Center*

Background:
Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy, most commonly associated with cortisol and/or androgen excess. Isolated mineralocorticoid hypersecretion in ACC is rare and typically attributed to aldosterone secretion or, more frequently, to excess production of mineralocorticoid active precursors such as 11-deoxycorticosterone (DOC) due to steroidogenic enzyme dysregulation. This entity may be overlooked, as aldosterone levels are not markedly elevated.

Case Presentation:
A 61 year old woman with a history of vitiligo and breast cancer presented with severe rhabdomyolysis, profound hypokalemia, and refractory hypertension. Evaluation revealed renal potassium wasting, suppressed renin, and low-normal aldosterone levels. Morning cortisol was low, with an abnormal cosyntropin 250 µg stimulation test, consistent with partial adrenal insufficiency. Androgens and estradiol were low, 17-hydroxyprogesterone was elevated, suggesting disordered steroidogenesis. Imaging demonstrated a 6.0 × 7.4 cm right adrenal mass with retroperitoneal lymphadenopathy and hepatic lesions. The patient required high dose mineralocorticoid receptor antagonists and aggressive potassium supplementation.
She underwent right adrenalectomy. Pathology reveled high grade ACC with lymphovascular invasion, necrosis, Ki 67 index 25%, Weiss score 7, positive margins (R1), ENSAT stage II disease. Early post operative recurrence of hypertension and hypokalemia occurred, imaging demonstrated unresectable retroperitoneal and hepatic mass. Systemic chemotherapy and immunotherapy were initiated.

Literature Review:
To date 8 cases of DOC secreting ACC have been reported (1974–2019). Patients typically presented with severe hypertension and hypokalemia mimicking primary aldosteronism, despite suppressed renin and normal or low aldosterone. Clinical outcomes were heterogeneous. Notably, 2 of 8 cases documented suppressed cortisol production, supporting disrupted steroidogenesis with diversion towards DOC synthesis.

Conclusion:
This case highlights a rare ACC phenotype characterized by severe mineralocorticoid excess and concomitant impaired cortisol synthesis, likely mediated by DOC rather than aldosterone. Recognition of DOC driven mineralocorticoid hypertension is essential, as reliance on aldosterone levels alone may be misleading, and life threatening adrenal insufficiency may coexist, with important diagnostic and therapeutic implications.

304

Long-Term Chronic Health Outcomes in CAYA Differentiated Thyroid Carcinoma Survivors and the Impact of Radioactive Iodine Therapy: A Real-World Study

Michal Yackobovitch-Gavan[1,2], **Rachel Bello Vitrial**[1], Tal Oron[1,3], Liora Lazar[1,3], Samah Hayek[4]

[1]*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*

[2]*Gray Faculty for Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel, Department of Epidemiology and Preventive Medicine School of Public Health*

[3]*Tel Aviv University, Tel Aviv, Israel, Gray Faculty for Medical and Health Sciences*

[4]*Deptartment of Epidemiology and Preventive Medicine*

School of Public Health, Gray Faculty for Medical and Health Sciences, Tel Aviv university, Tel Aviv, Israel

Context:
Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy among children, adolescents, and young adults (CAYA). Although survival exceeds 98%, data on long-term non-malignant chronic health conditions (CHC) are limited.

Objective:
To evaluate long-term, non-malignant CHC among CAYA DTC survivors compared with cancer-free controls and to assess associations with treatment-related factors, including radioactive iodine (RAI) exposure.

Design, Setting, and Participants:
Retrospective population-based cohort study using longitudinal electronic medical records from Clalit Health Services, Israel (1982–2022). The cohort included 5,267 individuals diagnosed with DTC before age 40 and 21,062 matched cancer-free controls. Median follow-up was 14.7 years.

Main Outcome Measures:
Incidence of non-malignant CHC occurring ≥2 years after diagnosis across metabolic, cardiovascular, renal, hepatic, gastrointestinal, pulmonary, skeletal, autoimmune/rheumatologic, and emotional domains, with hazard ratios estimated using Cox proportional hazards models.

Results:
Overall CHC risk was similar between DTC survivors and controls (HR 1.05; 95% CI, 1.00–1.11); however, survivors were less often CHC-free (45.6% vs. 48.0%) and more likely to develop multimorbidity (≥2 conditions; 35.7% vs. 32.0%); single comorbidity incidence was similar (17.8% vs. 19.2%). Survivors had higher BMI (26.2 vs. 25.5 kg/m²; P0.001), greater obesity prevalence (27.2% vs. 23.6%), and increased risks of dyslipidemia and hypertension (each HR 1.14), stroke (HR 1.22), chronic kidney disease (HR 1.57), gastroesophageal disorders (HR 1.21), and osteopenia/osteoporosis (HR 1.47), while pulmonary, autoimmune, hepatic, and emotional morbidities were similar. RAI therapy was associated with a dose-dependent increase in comorbidity risk (HR 1.20 with one course; HR 1.33 with ≥2 courses) and earlier, more CHCs.

Conclusions: Despite excellent survival, CAYA DTC survivors face an increased long-term burden of multisystem non-malignant CHCs, strongly associated with RAI exposure in a dose-dependent manner. Long-term follow-up strategies should incorporate risk-adapted monitoring and consideration of treatment de-escalation when appropriate.

305

The association between CGM derived glycemic control meassures at different gestational periods among women with pregestational T1D and the risk of neonatal hypoglycemia

Noam Brakin Lederer[1], Tali Cukierman-Yaffe[1]
Endocrinology, Sheba Medical Center

Background: Research shows that type 1 diabetes (T1D) is associated with increased risk for perinatal and neonatal complications. Hypoglycemia is a common neonatal complication associated with glycemic control throughout pregnancy. Previous studies have shown that increased HbA1c in late pregnancy and poor glycemic control were associated with neonatal hypoglycemia. However, it remains unclear which gestational period is critical for glucose control to reduce neonatal hypoglycemia risk. Moreover, few studies have used data from continious glucose monitoring (CGM) systems to determine the association between glycemic control and neonatal hypoglycemia at different gestational periods.

Aim: This study aimed to evaluate the association between glycemic control at different gestational periods and the risk of neonatal hypoglycemia among patients with pregstational T1D, using CGM measures.

Methods: This study included 110 singleton pregnancies among 76 patients with pregestational T1D who were monitored at the High Risk Pregnancy Clinic and delivered at the Sheba Medical Center between May 5th 2011 and April 11 2022. Patients for whom CGM data during pregnancy and neonatal blood glucose was available were included. Data on each pregnancy was collected from patients' medical records, including demographic and clinical information, as well as neonatal hypoglycemia that required IV treatment. CGM data were downloaded from patient sensors at each clinic visit. The raw data was extracted and time in range (TIR; 63-140 mg/dL) and time above range (TAR; 140 mg/dL) as well glucose variability (standard deviation) were calculated for each trimester. Data was statistically analyzed using logistic regression, with neonatal hypoglycemia that required IV the dependent variable and glucose indices the independent variable.

Results: Among the singelton pregnancies of patients with pregstational T1D, lower TIR (60.1% vs. 67.5%, p=0.004), higher TAR (22.9% vs. 30.4%, p=0.005), and lower glucose variability (42.7 vs. 48, p=0.04) during the second trimester were associated with the risk of neonatal hypoglycemia. In the third trimester, lower TIR (63.1% vs. 69.5%, p=0.03) was associated with neonatal hypoglycemia risk.

Discussion: In our cohort of singleton pregnancies of women with pregestational T1D, glycemic control during the second and third trimesters was associated with the risk of neonatal hypoglycemia, whereas first trimester glycemia was not. These findings suggest that mid and late gestational glucose exposure may be of particular importance for fetal hypoglycemia. Generalizability of these results may be limited due to the small sample size. Further research with larger samples at multiple institutions is required.

307

HLA Genotype, BMI Status, and Young-adult-onset Type 1 Diabetes

Cole Bendor[1], Aya Bardugo[1], Amir Tirosh[2], Sapir Israeli[3], Estela Derazne[4], Inbar Zucker[5], Miri Lutski[5], Ariel Furer[1], Zivan Aviad-Beer[1], Orit Pinhas-Hamiel[2], Gabriel Chodick[4], Bracha Zisser[6], Arnon Afek[2], Hertzel Gerstein[7], Tali Cukierman-Yaffe[2], Sigal Manor[6], Yoram Louzoun[3], Gilad Twig[2]

[1]*Israel Defense Forces*
[2]*Sheba Medical Center*
[3]*Bar-Ilan University*
[4]*Tel-Aviv University*
[5]*Israel Ministry of Health*
[6]*Ezer Mizion Bone Marrow Donor Registry*
[7]*McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada*

BACKGROUND
Obesity is increasingly recognized as a risk factor not only for type 2 diabetes but also for type 1 diabetes (T1D). Its interaction with genetic susceptibility, particularly in adult-onset T1D, remains unclear.
METHODS
We conducted a population-based cohort study of 604,968 Israeli adolescents (aged 16–19 years; 44% females) evaluated between 1996 and 2016 and followed for incident T1D. HLA genotyping was performed at baseline; high-risk HLA was defined by the presence of predetermined class I or II risk alleles. Body mass index (BMI) was measured at adolescence and categorized using the 85th percentile as a cutoff. Cox proportional hazards models estimated hazard ratios (HRs) with 95% confidence intervals (CIs). Interaction between HLA risk and BMI was assessed.
RESULTS
During 4.8 million person-years of follow-up (mean, 7.9 years), 151 participants developed T1D. A significant additive interaction between HLA risk and BMI was observed (relative excess risk due to interaction, 4.79; 95%CI, 1.16–8.41; P=0.010). Compared to adolescents with standard-risk HLA and lean BMI, adjusted HRs for T1D were 0.56 (95%CI, 0.13–2.40) for standard-risk HLA with high BMI, 4.59 (95%CI, 2.77–7.60) for high-risk HLA with lean BMI, and 8.94 (95%CI, 5.07–15.75) for high-risk HLA with high BMI. Participants with high-risk alleles in both class I and II loci and high BMI had a 25.77-fold increased risk (95%CI, 13.27–50.05).
CONCLUSIONS
HLA genotypes and adolescent BMI interact to substantially increase the risk of adult-onset T1D. These findings may inform population risk stratification and screening strategies.

Treatment-Resistant Insulin Autoimmune Syndrome Associated with Methimazole in Graves' Disease

Karina Rozenfeld[1], **Gidaa Ayada**[1], Riad Taher[1], Amir Bashkin[2], Hibi Assala[3], Sagit Zolotov[4]

[1]*Institute of Endocrinology, Diabetes and Metabolsim, Rambam Health Care Campus*

[2]*Endocrinology Unit, Galilee Medical Center*

[3]*Internal Medicine Department, Galilee Medical Center*

[4]*Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus*

Background

Insulin Autoimmune Syndrome (IAS), also known as Hirata disease, is a rare cause of spontaneous hypoglycemia characterized by circulating insulin autoantibodies in individuals without prior exposure to exogenous insulin. IAS is predominantly reported in Asian populations, with fewer than 10% of cases described in Western countries. The syndrome may be idiopathic or drug-induced; among the latter, methimazole is the most frequently implicated agent.

Case Presentation

We report the case of a 21-year-old Arab woman admitted to an internal medicine department following an initial episode of severe hypoglycemia complicated by loss of consciousness (plasma glucose 18 mg/dL). A year before this episode the patient was diagnosed with Graves' disease and treated intermittently with methimazole. Two months after reinitiation of methimazole (20 mg/day), the patient developed recurrent episodes of postprandial hypoglycemia. During a documented hypoglycemic episode (plasma glucose 27 mg/dL), laboratory evaluation revealed markedly elevated serum insulin (136,009 pmol/L; reference 17.8–173 pmol/L) and C-peptide (27,392 pmol/L; reference 366–1,466 pmol/L). Screening for sulfonylureas was negative, and pancreatic imaging was unremarkable. Diagnosis of IAS was confirmed by markedly elevated insulin autoantibody titers (100 U/mL; positive 10 U/mL).

Management and Outcome

Hypoglycemia was refractory to intravenous dextrose, high-dose glucocorticoids, intravenous immunoglobulin, and octreotide. Clinical stability was achieved following the initiation of diazoxide (75 mg three times daily) in conjunction with frequent, low-carbohydrate meals, resulting in the complete resolution of hypoglycemic episodes. Diazoxide was successfully tapered and discontinued after six months without symptomatic recurrence. Given the severity of the initial presentation and the risks associated with alternative thionamides, propylthiouracil was avoided; instead, definitive management of Graves' disease was achieved via a successful total thyroidectomy.

Conclusion

This case underscores a rare presentation of methimazole-induced IAS characterized by severe, treatment-resistant hypoglycemia. Our findings suggest that diazoxide may offer a potent therapeutic alternative in refractory cases where standard immunosuppressive therapy fails. Clinicians should maintain a high index of suspicion for IAS in patients with Graves' disease who develop spontaneous hypoglycemia during methimazole treatment.

309

Triangulating HDL traits across outcomes identifies ANGPTL4 as a pathway linked to lower myocardial infarction risk and increased lifespan

Elad Shemesh, Guillaume Pare[1]
McMaster University

Background: Associations of HDL cholesterol (HDL-C) with ASCVD and mortality are inconsistent and even paradoxical, suggesting HDL-C may be an imperfect surrogate for HDL biology. HDL particle concentration (HDL-P) and HDL size capture distinct dimensions of HDL metabolism (particle abundance vs remodeling) and may better localize actionable pathways.
Methods: In ASCVD-free individuals (n= 523,776; UK Biobank and All of Us databases), we evaluated adjusted associations of HDL-C, HDL-P, and HDL size with incident ASCVD, incident MI, and all-cause mortality. We then prioritized HDL genes and applied a three-layer triangulation framework: (1) observational HDL trait–outcome patterns, (2) UK Biobank gene-centric two-step Mendelian randomization linking cis-variant effects on HDL traits to parental survival mediated through those traits, and (3) external validation of aligned cis-instrument effects on clinical endpoints in FinnGen (n = 520,000 individuals).
Results: In UK Biobank, low HDL-C, HDL-P, and HDL size were consistently associated with higher ASCVD and MI risk (e.g., HDL-C: ASCVD OR 1.45; MI OR 1.54). Mortality associations diverged across HDL metrics: high HDL-C and high HDL-P were associated with higher all-cause mortality (HDL-C OR 1.18; HDL-P OR 1.13), whereas high HDL size was associated with lower mortality (OR 0.76). Across genetic triangulation, ANGPTL4 emerged as the most convergent gene across HDL traits and outcomes. In FinnGen, the ANGPTL4 cis-instrument showed concordant protection for MI across HDL traits (HDL-P OR 0.38 [95% CI 0.24–0.60]; HDL size OR 0.43 [0.29–0.64]); stroke showed concordant pattern. UK Biobank two-step Mendelian Randomization supported concordant gene-level effects on parental lifespan mediated through HDL traits.
Conclusions: HDL traits show outcome-specific patterns: low HDL-C, HDL-P, and HDL size associate with higher ASCVD/MI risk, whereas at high levels HDL-C and HDL-P associate with higher mortality while larger HDL size associates with lower mortality. Genetic triangulation across UK Biobank and FinnGen implicates ANGPTL4-linked HDL particle traits in lower MI risk and supports ANGPTL4 as a candidate pathway connecting HDL biology to survival.

311

Inflammatory Biomarkers as Predictors for 90-Day Mortality in Hospitalized Patients with Amiodarone-Induced Thyrotoxicosis - A Historical Cohort Study

Tali Epstein Weiss[1,2], Tomer Ziv-Baran[3], Eugene Feigin[1,2], Yona Greenman[1,2], Elena Izkhakov[1,2]

[1]*Institute of Endocrinology, Diabetes, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel*

[2]*Gray Faculty of Medical and Health Sciences, Tel Aviv*

[3]*Department of Epidemiology and Preventive Medicine, School of Public Health, Gray Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

Background: Amiodarone-induced thyrotoxicosis (AIT) is associated with high mortality rates, especially in patients with underlying severe cardiac disease. The prognostic value of inflammatory biomarkers for predicting 90-day mortality remains uncertain. This study evaluates their potential utility as predictive markers.

Methods: This historical-prospective cohort study was conducted at a large tertiary medical center and included all consecutive patients aged ≥18 years hospitalized with AIT between January 2015 and December 2023. Data on demographics, clinical characteristics, admission laboratory results, AIT-specific therapy, and 90-day all-cause mortality were collected. Inflammatory biomarkers were calculated using laboratory test results obtained at admission. The discriminative ability of each biomarker was evaluated using a receiver operating characteristic curve, and DeLong's test was used to compare the areas under the curve (AUCs). A classification and regression tree (CART) model was employed to identify patient subgroups at increased mortality risk. A sensitivity analysis was performed in patients with severe biochemical thyrotoxicosis.

Results: The study included 209 patients (mean age 71 ± 13 years; 42.6% female), of whom 96 (45.9%) died within 90 days. Patients who died exhibited significantly higher inflammatory burden at admission. All inflammatory biomarkers (neutrophil-to-lymphocyte ratio [NLR], C-reactive protein-to-lymphocyte ratio [CLR], and multi-inflammatory index [MII]) were significantly elevated in non-survivors. Among these, CLR demonstrated the highest discriminatory ability for 90-day mortality in the overall cohort (AUC = 0.705), while all three biomarkers showed strong performance in the sensitivity analysis (AUCs 0.709–0.744). CART analysis identified distinct mortality risk groups based on MII and CLR thresholds, with mortality rates ranging from 12% to over 70%. Traditional demographic factors and comorbidities were not independently associated with short-term mortality.

Conclusions: This study identified a significant association between the inflammatory biomarkers CLR, NLR, and MII assessed at hospital admission and 90-day mortality in patients hospitalized with AIT. These biomarkers are readily accessible through routine blood tests, and they may facilitate early risk stratification and inform clinical decisions regarding targeted interventions and close clinical follow-up.

313

A Disappearing Diabetes: Extreme Stress Hyperglycemia During an Ulcerative Colitis Flare

Hitam Hagog Natour, Michal Kasher Meron, Pnina Rotman-Pikielny, Liat Barzilay Yoseph

Background

Stress hyperglycemia can accompany acute illness; however, extreme hyperglycemia with markedly elevated hemoglobin A1c (HbA1c) in individuals without pre-existing diabetes is rare and may mimic new-onset diabetes. Severe inflammatory states, such as active ulcerative colitis (UC), can disrupt glucose homeostasis through inflammation driven insulin resistance and through activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system.

Case Description

A 56-year-old man with BMI 28, previously healthy, with no personal history of diabetes but a strong family history of type 2 diabetes, was admitted with severe chronic diarrhea, abdominal pain, and weight loss. He was hemodynamically stable but had extreme hyperglycemia (~600 mg/dL) without metabolic acidosis. HbA1c was 9.4%, despite a documented normal value of 5.08% two months earlier. Autoimmune diabetes evaluation, including anti-GAD, IA-2, were negative. Insulin and C-peptide levels were preserved, with elevated HOMA-IR, consistent with severe insulin resistance. The exocrine function was preserved with normal elastase levels in the stool. Inflammatory markers were mildly elevated. Abdominal CT excluded pancreatic masses or structural lesions while suggesting colitis. Colonoscopy and histopathology confirmed active moderate UC. He was treated with intravenous corticosteroids and basal–bolus insulin. With clinical improvement, glycemia rapidly normalized, allowing insulin discontinuation. Following steroid taper and initiation of mesalamine, he achieved sustained UC remission. At three-month follow-up, continuous glucose monitoring showed persistent euglycemia (85–110 mg/dL) without therapy, and HbA1c normalized to 4.7%.

Conclusion

This case highlights that severe inflammation during an active ulcerative colitis flare can induce profound but fully reversible hyperglycemia via inflammation driven insulin resistance and HPA axis activation, mimicking new-onset diabetes. Awareness of this phenomenon is essential to avoid misdiagnosis and unnecessary long-term therapy, while emphasizing the need for follow-up given the increased future risk of diabetes.

Glucosamine links hyperglycemia to mTORC1 activation and glucose toxicity in diabetes

Ziv Teselpapa[1], Yael Riahi[1], Aviram Kogot-Levin[1], Elisheva Zemelman[1], Fatema Gamal[1], Tamar Cohen[1], Dana Avrahami[1], Erol Cerasi[1], Erez Dror[2], Gil Leibowitz[1]

[1]*Diabetes Unit and Endocrine Service, Hadassah Medical Center of the Hebrew University, Jerusalem, Israel*

[2]*2Department of Developmental Biology and Cancer Research, The Institute for Medical Research Israel-Canada (IMRIC), The Hebrew University-Hadassah Medical School, Jerusalem, Israel*

Introduction

In diabetes, chronic hyperglycemia drives β cell dysfunction and multi-organ complications. A key mechanism is mTORC1 overstimulation, leading to impaired glucose metabolism, ER stress, oxidative stress, and inflammation. However, the upstream metabolic signals linking glucose to mTORC1 activation remain unclear. We identify glucosamine as a key metabolite connecting elevated glucose to mTORC1 signaling and β-cell dysfunction. Glucosamine is a key substrate in the hexosamine biosynthetic pathway (HBP), which produces UDP-GlcNAc, the donor for protein O-GlcNAcylation, recently implicated in epigenetic regulation.

Methods

mTORC1 activity and localization were assessed by Western blotting and immunostaining. Oxidative stress was evaluated using RT-qPCR and MitoTracker staining with the anti-scavenger MitoTempo. Epigenetic modulation was assessed by flow cytometric analysis of H3K27me3. Single-nucleus Multiome profiling (10x Genomics, snRNA-seq and ATAC-seq) was performed on nuclei isolated from dispersed pancreatic islets.

Results

In vitro and in vivo metabolic assays demonstrated that glucosamine induced mTORC1 activation, evident by increased phosphorylation of S6 and 4EBP1, increased oxidative stress, and reduced β cell viability, highlighting its potential pathological role in diabetic islets.

Glucosamine treatment induced epigenetic remodeling in β cells, characterized by elevated levels of the repressive histone mark H3K27me3. Notably, this increase mirrors the enhanced H3K27me3 enrichment observed in various diabetic models.

snRNA-seq analysis revealed that glucosamine treatment upregulated genes involved in growth factor-mediated mTORC1 signaling, e.g. Igf1R, Pikfye, a lipid kinase that synthesizes PI3P and Fnip1, as well as genes regulating calcium signaling, e.g. calcineurin and calcium calmodulin. In parallel, key genes associated in the ER stress response (unfolded protein response), including Hspa5 (Bip), Ern1 (Ire1α) and Atf6 were upregulated, whereas key genes regulating β-cell function and differentiation, including Pdx1, Nkx6.1, Mafa, Glp1r and Ins1/2 were downregulated.

Conclusion

Prolonged exposure to glucosamine activates mTORC1, disrupts mitochondrial function and calcium homeostasis, resulting in oxidative stress, ER stress, β-cell dysfunction and dedifferentiation. Collectively, these alterations reflect key features of β-cell dysfunction in diabetes.

317

Hyperglucagonemia contribute to the pathophysiology of diabetic kidney disease by activating mTOR signaling in kidney proximal tubule cells

Fatema Gamal[1]
Diabetes Unit and Endocrine Service, Hadassah Medical Center of the Hebrew University, Jerusalem, Israel

Diabetic kidney disease (DKD) is a major complication of diabetes that is partially mediated via metabolic stress in kidney proximal tubule cells (KPTCs). Hyperglucagonemia is a common feature of diabetes; however, its role in mediating DKD is not clear. We have previously shown in a mouse model of type 1 diabetes (T1D) that the nutrient sensor mTOR is an important mediator of DKD.

Aim: To study how glucagon regulates mTOR signaling in physiology and in diabetes and its impact on the development of DKD.

Methods: Glucagon–mTOR signaling was studied in mice and primary KPTCs. mTORC1/2 activity and pyruvate dehydrogenase (PDH) phosphorylation were assessed by immunoblotting and immunostaining. Pathway specificity was examined using pharmacological inhibition of insulin signaling, SGLT2, PKA, and mTOR. Cellular respiration and glycolysis were measured by Seahorse analysis. Metabolic flux and targeted metabolomics were performed following $^{13}C_6$-glucose labeling. Gene expression was analyzed by qPCR.

Results: In vivo, acute administration of glucagon activated both mTORC1 and mTORC2 in kidney cortex extracts, evidenced by increased phosphorylation of S6 and 4EBP1 (downstream target of mTORC1) and Akt(s473) (downstream target of mTORC2) by western blotting and immunofluorescence staining. Pre-treatment with the insulin receptor antagonist S961 or with the SGLT2i dapagliflozin did not prevent mTOR activation by glucagon, indicating that this effect is independent of insulin and hyperglycemia. In primary KPTCs under low-glucose (LG) conditions, glucagon similarly activated mTORC1/2, an effect abolished by the PKA inhibitor H-89. Seahorse analysis and $^{13}C_6$-glucose tracing showed that at LG, glucagon suppressed glucose oxidation and mitochondrial respiration while enhancing gluconeogenic flux. Mechanistically, glucagon increased the PDH phosphorylation in an mTORC2-dependent manner, thereby inhibiting PDH activity and limiting pyruvate entry into the TCA cycle. Of note, high glucose (HG) induced sustained PDH phosphorylation and blunted the response to glucagon, yet treatment with glucagon at HG upregulated the expression of gluconeogenic enzymes.

Conclusion: Glucagon is a central regulator of mTORC1/2 signaling in KPTCs. We suggest that glucagon signaling via mTORC2-PDH is an adaptive response to fasting. Exposure to hyperglycemia induces sustained activation of this pathway leading to metabolic inflexibility, which may contribute to the development of DKD.