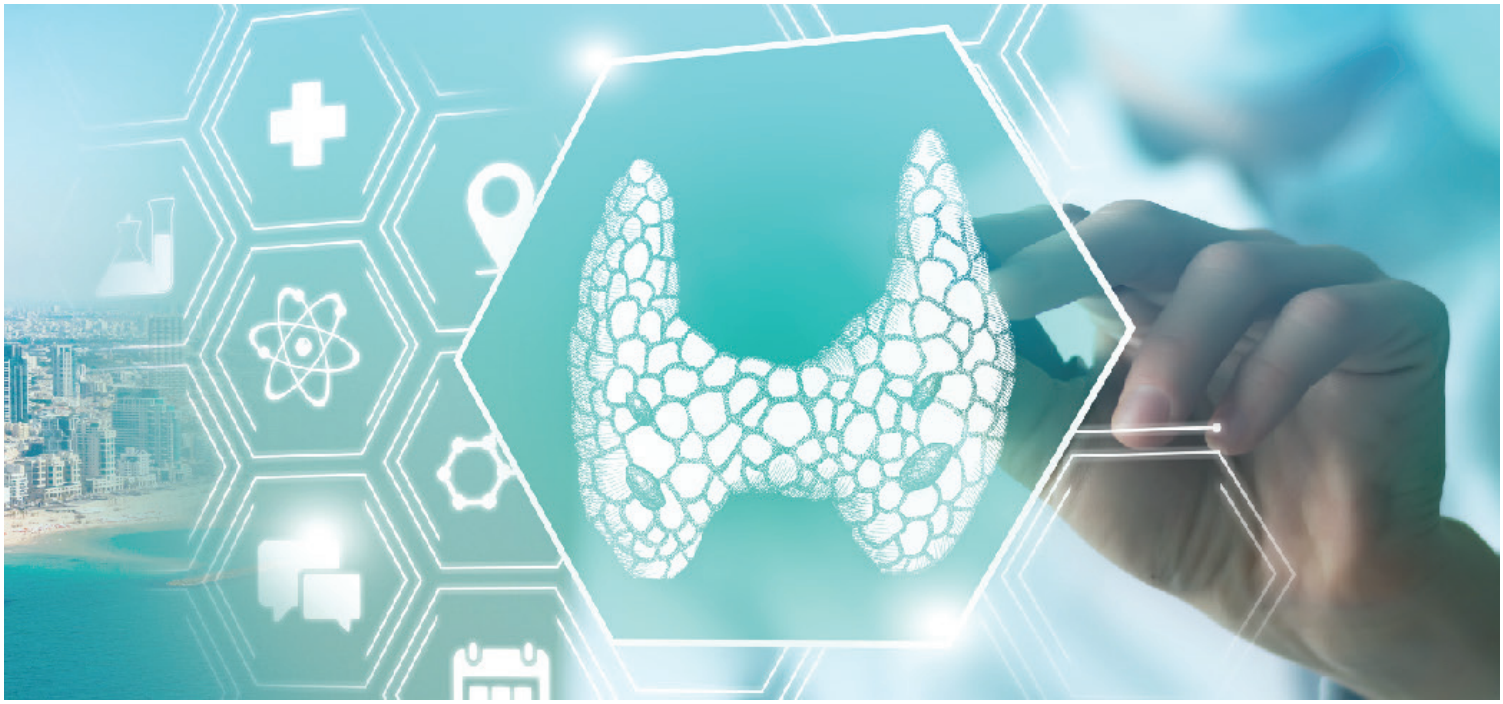
האגודה הישראלית לאנדוקרינולוגיה
Israel Endocrine Society

THE 52TH ANNUAL MEETING OF THE ISRAEL ENDOCRINE SOCIETY (IES)



PROGRAM BOOK

InterContinental David Hotel, Tel Aviv | April 1-2, 2024

שלום חברים,

ברוכים הבאים לכנס המדעי ה- 52 של האגודה הישראלית לאנדוקרינולוגיה המתקיים ב- 1-2.4 במלון דיויד אינטרקונטיננטל בתל אביב.

השנה שוב למדנו כמה המפגש השנתי שלנו איננו מובן מאליו. אנו מוקירים תודה על האפשרות להיפגש, לעסוק במדע וברפואה ולחזק את תחום האנדוקרינולוגיה בישראל בייחוד בתקופה קשה ומורכבת זו.

הכנס השנה אינו סטנדרטי. הוא מכיל הרבה מהתכנים שהיו אמורים להיות מוצגים בכנס החורף שבוטל בשל המלחמה.
השתדלנו לשמור על האיזון המתאים בין הנושאים הקליניים והמחקר הבסיסי על מנת שכולם יוכלו למצוא עניין ולהתעדכן.

לשמחתנו, למרות המצב, הוגשו לכנס כמאה תקצירים. תוכלו להנות מעבודות חדשניות ומעניינות במושבים השונים.

אנו מודים למרצים האורחים על תמיכתם וחברותם ועל שלא היססו להגיע הנה למרות המלחמה. תודה למרצים המקומיים על תרומתם המשמעותית להצלחת הכנס.

תודה מיוחדת לרועי גרסון מחברת zoomIn שמנצח על מלאכת ארגון הכנס בסבלנות, ובמקצועיות רבה.

קיווינו מאוד שעד מועד קיום הכנס ישככו קולות הלחימה, שהחטופים ישובו ושנדע ימים שקטים יותר.
כולנו תפילה שנזכה לכך בקרוב.

פרופ'' גיל ליבוביץ

נשיא האגודה הישראלית
לאנדוקרינולוגיה

ד"ר יעל קופרמן

יו"ר כנס האביב

ד"ר יואל טולדנו

יו"ר כנס שותף -
כנס החורף

ד"ר מרב פרנקל

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לאנדוקרינולוגיה

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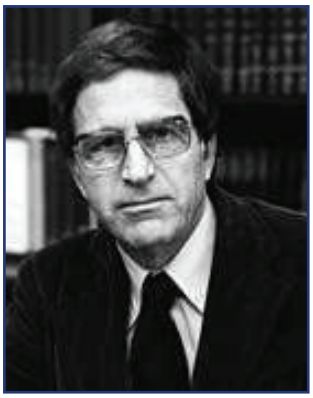
פרופ' הנס יוחנן לינדנר ז"ל - מילים לזכרו



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.

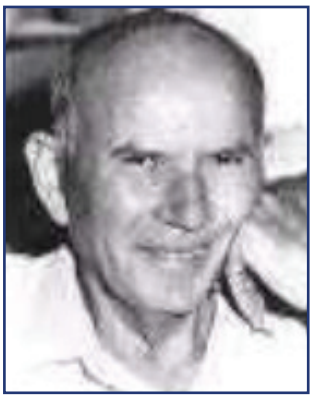
בשנת 1979 הוענק לו פרס ישראל במדעי החיים והוא נבחר כחבר באקדמיה הישראלית למדעים. בשנת 1982 הוענקו לו פרס רוטשילד בביולוגיה וכמו כן, פרס Axel-Munthe בשטח הביולוגיה של הפוריות.

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

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

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

Invited Speakers

Dr. Giovanni Corona

Giovanni Corona works as an endocrinologist and andrologist at the Endocrinology Unit of Maggiore-Bologna Hospital, Bologna, Italy. He is the co-author of more than 450 peer-reviewed manuscripts, various book chapters and invited reviews in the field of endocrinology and sexual medicine. From July 2010 to December 2015, he was nominated for an Associate Editor of the Journal of Sexual Medicine. Since January 2017 he was re-appointed as the Associate Editor of the Journal of Sexual Medicine. President of the Italian Society of Andrology and Sexual Medicine 2018-2021. Since 2018-2002 he was nominated as the Chair of the scientific committee of the European Society for Sexual Medicine. Since 2021 he was appointed as a Secretary of the International Society of Andrology. Since 2023 he is nominated as the President of the European Society for Sexual Medicine.

Prof. Daniel Drucker

Prof. Drucker is an Endocrinologist and Professor of Medicine in the Division of Endocrinology at University of Toronto. He holds the Banting and Best Diabetes Centre-Novo Nordisk Chair in Incretin Biology. His laboratory is based in the Lunenfeld Tanenbaum Research Institute at Mount Sinai Hospital in Toronto and studies the molecular biology and physiology of the glucagon-like peptides. His discoveries have enabled development of several new therapies for the treatment of diabetes, obesity and intestinal failure. Drucker has received numerous international awards for his translational science and has been elected to Fellowship in the Royal Society (London) and the National Academies of Sciences and Medicine (USA).

Prof. Decio L. Eizirik

Decio L. Eizirik, M.D., Ph.D., is Professor at the ULB Center for Diabetes Research (https://www.ucdr.be/), Brussels, Belgium. He has published >420 full papers with an h-index of 92. He has received several national and international prizes, including the JDRF "Diabetes Care Research Award", 1998; the EASD "Albert Renold Prize Lecture", 2012; the nPOD "George Eisenbarth Award and Memorial Lecture", 2023; and was scientific secretary of the EASD. His research focus on the mechanisms of pancreatic beta cell dysfunction and death in type 1 diabetes.

Dr. Joshua Klopper

Dr. Klopper joined Veracyte in 2021 after serving as the Regional Service Chief for the Department of Endocrinology of Colorado Permanente Medical Group of Kaiser Permanente for four years. His post-graduate medical training included an internal medicine residency, post-doctoral research fellowship and endocrinology fellowship at The University of Colorado School of Medicine, where he joined the faculty in 2006 as an Assistant Professor of Medicine. He focused on thyroid cancer as a translational scientist looking at novel molecular targets for treating advanced thyroid cancer and was an investigator on an early clinical utility study of the original Afirma gene classifier for reducing unnecessary surgeries in thyroid nodules with indeterminate cytology.
Dr. Klopper was promoted to Associate Professor of Endocrinology and Radiology prior to transitioning to Kaiser in 2015. Nationally, Dr. Klopper was the co-director of the Endocrine Society Introductory Hands-On Thyroid Ultrasound Workshop for five years and has served on the American Thyroid Association board of directors.

Prof. Bente Langdahl

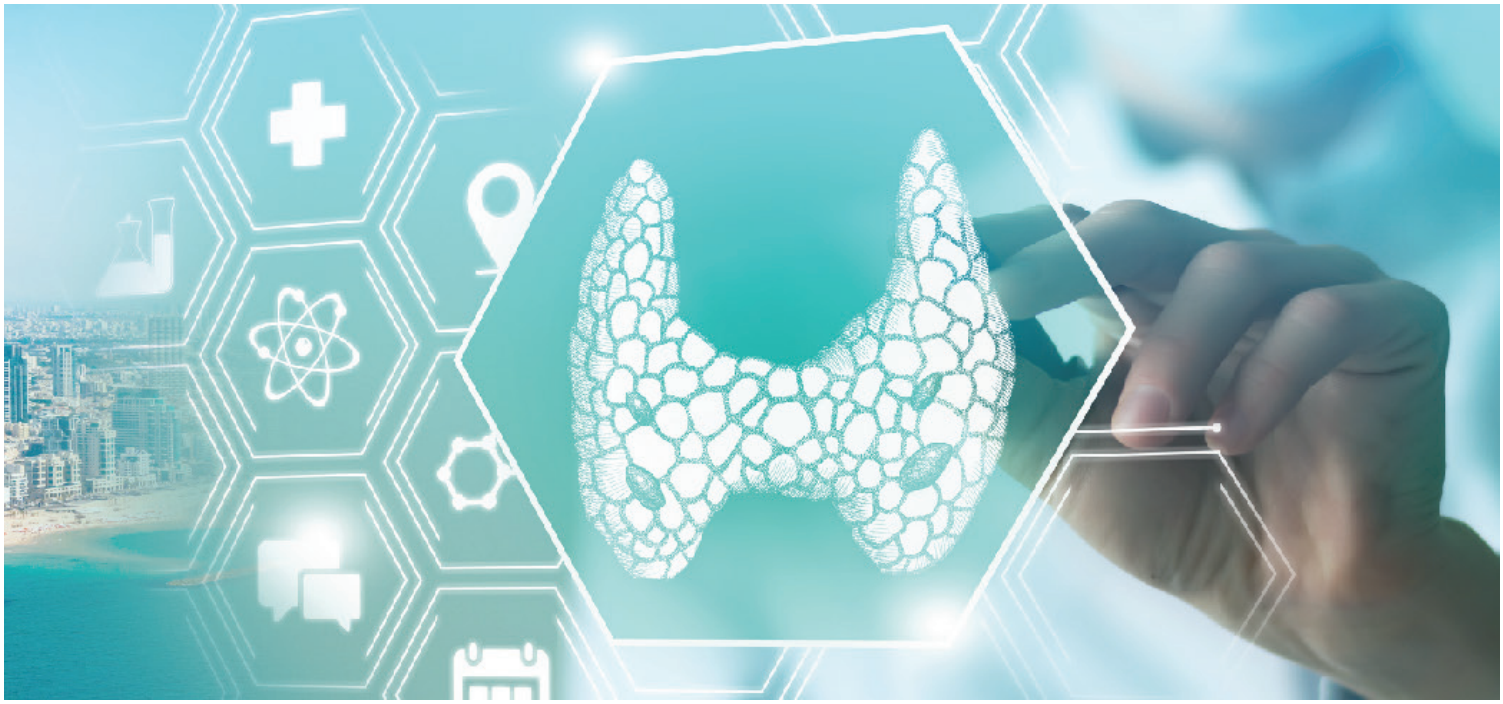
Bente Langdahl is Professor at Aarhus University and the Department of Endocrinology at Aarhus University Hospital, Denmark. She graduated from the medical school at Aarhus University in 1988 and did her clinical training endocrinology at Aarhus University Hospital. She attained her PhD: "Investigations on a possible pathogenic role of thyroid hormones in postmenopausal osteoporosis". and her DMSc: "The genetics of bone mass and risk of osteoporotic fractures" at Aarhus University.
Bente Langdahl's main research interests are the development of new treatments and the long-term management of osteoporosis, the impact of diabetes, thyroid diseases, and HIV on bone health, and osteogenesis imperfecta in adults.
Bente Langdahl has received the ECTS Philippe Bordier Award, the ASBMR Federic Bartter Award and the DBS Mosekilde Award. Bente Langdahl is past-president of ECTS and past-chair of IFMRS.

Prof. Matthias Tschöp

Matthias Tschöp is the CEO of Helmholtz Munich, Vice President of the German Helmholtz Association and Alexander-von-Humboldt Professor at the Technical University of Munich. Tschöp unraveled fundamental gut-brain signals to discover the first highly effective drugs for human obesity in collaboration with the chemist Richard DiMarchi - the dual and triple gut hormone multi-agonists. A first representative is FDA-approved, others are successfully progressing through clinical trials. Tschöp has received numerous honors and awards, including the Banting Medal (2023), the Heinrich Wieland Prize (2023), the Schering Prize (2023), and the EASD-Lilly Centennial Prize (2022) and the Ernst Jung Prize (2021). He holds an adjunct professorship at Yale University and an honorary doctorate at Leipzig University. He was elected a member of the German, Bavarian, and European Academies of Sciences, the American Society for Clinical Investigation and the Association of American Physicians.

האגודה הישראלית לאנדוקרינולוגיה
Israel Endocrine Society

THE 52TH ANNUAL MEETING OF THE ISRAEL ENDOCRINE SOCIETY (IES)



SCIENTIFIC PROGRAM

Monday, April 1st

07:30-08:15 **Registration, Refreshments & Visit the Exhibition**

Morning Meditation

08:15-09:45 **Parallel Sessions**
Abstracts: Body Composition

Hall A

Chairs: **Prof. Yossi Tam**, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, the Hebrew University of Jerusalem
Dr. Idit Dotan, Head, Diabetes and Obesity Services, Endocrinology and Metabolism Division, Rabin Medical Center, Beilinson Campus

08:15-08:27 **Adipose Tissue Histopathology as a Putative Basis for Advancing Personalized Management of Obesity**

PhD Student Marina Rosengarten Levin[1,2], Dr. Yulia Haim[1], Dr. Alexandra A. Tsitrina[1,3], MD/PhD Student Habib Mualem[1], MD/PhD Student Alon Zemer[1], Dr. Yair Pincu[1], Dr. Idit F. Liberty[4,5], Dr. Oleg Dukhno[5,6], Prof. Assaf Rudich[1], Dr. Uri Yoel[1,7]

[1]Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel
[2]Maccabi Health Care Services, Israel
[3]Ilse Katz Institute for Nanoscale Science and Technology, Ben-Gurion University of the Negev, Israel
[4]Diabetes clinic, Soroka University Medical Center, Israel
[5]Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel
[6]Surgical word B, Soroka University Medical Center, Israel
[7]Endocrinology, Soroka University Medical Center, Israel

08:27-08:39 **Body Mass Index in Late Adolescence and The Risk for Disabling Morbidity in Early Young Adulthood**

Dr. Yair Zloof[1,2,3], **Maya Karen Nitecki**[1,2,4], Dr. Ofek Adara[1], Dr. Avishai M. Tsur[2,5,6], Dr. Estela Derazne[7], Dr. Dorit Tzur[1], Dr. Jacob Rotschielda[1], Dr. Maya Brauna[1], Dr. Orit Pinhas-Hamiel[7,8], Dr. Naomi Fliss Isakov[2,9], Dr. Hadar Milloh-Razf[7,10], Dr. Dan Nemetf[7,11], Dr. Dror Dickerf[7,12], Dr. Avi Moyal[13], Dr. Oded Scheuermanc[7,14], Dr. Zivan Beer[1], Dr. Marius Braunf[7,15], Dr. Arnon Afek[7,16], Dr. Gilad Twig[1,2,10,17]

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[3]Schneider Children's Medical Center of Israel , Petach Tikva, Israel
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[7]Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
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[9]hNutrition, MOH Israel, Tel Aviv, Israel
[10]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel
[11]Child Health and Sports Center, Pediatric Department, Meir Medical Center, Kfar-Saba, Israel
[12]Department of Internal Medicine D, Hasharon Hospital Rabin Medical Center, Petah Tikva, Israel
[13]School of Education, Ono Academic College, Kiryat Ono, Israel
[14]Schneider Children's Medical Center of Israel, Petach Tikva, Israel
[15]mThe Liver Institute, Rabin Medical Centre, Beilinson Hospital, Petah-Tikva, Israel
[16]nSheba Medical Center, Central Management, Tel Hashomer, Ramat Gan, Israel
[17]Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

08:39-08:51 **CT-Based Sarcopenia Assessment: Predicting Outcomes in Acute Infection Patients**

Dr. Matan Elkan[1], Dr. Lior Cochavi, Dr. Alla Khashper, Dr. Eli Kravchick, Dr. Ella Kravitz, **Ronit Koren**[1]

[1]Internal Medicine A, Shamir Medical Center, Israel

08:51-09:03 **Low Dose Estradiol Gender-Affirming Hormone Therapy (GAHT) Generates Rapid Feminizing Body Changes in Transgender Women: A Dual Energy X-Ray Absorptiometry-Based Prospective Study**

Dr. Iris Yaish[1], Med. Student Guy Gindis[1,2], PhD Assaf Buch[1,3], Dr. Yael Sofer[1,2], Prof. Yona Greenman[1,2], BSc Mira Arbiv[1], RN, BA Yaffa Moshe[1], Karen Tordjman[1,2]

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[2]Faculty of Medicine, Tel Aviv University, Israel
[3]Department of Nutrition Sciences, Ariel University, Israel

09:03-09:15 **Changes in Weight and BMI Following Treatment for Cushing Syndrome: Long-Term Outcomes and Potential Predictors**

Liat Sasson[1,2], Dr. Laura Dery[1], Dr. Julia Stern[1], Dr. Ilan Shimon[1,2], Dr. Yaron Rudman[1,2], Dr. Shiri Kushnir[3], Prof. Amit Akirov[1,2]

[1]Tel Aviv University, Sackler School of Medicine, Tel Aviv, Israel
[2]Rabin Medical Center, Beilinson Hospital, Institute of Endocrinology, Petach Tikva, Israel
[3]Rabin Medical Center, Beilinson Hospital, Research Authority, Petach Tikva, Israel

09:15-09:27 **Muscle-to-Fat Ratio in Children and Adolescents with Type 1 Diabetes in Predicting Glycemic Control and Partial Clinical Remission**

Shay Averbuch[1,2], Ms. Michal Yackobovitch-Gavan[3], Mr. Asaf Ben Simon[1,2], Ms Hagar Interator[1,4], Ms. Adar Lopez[1,4], Ms. Ophir Borger[1,4], Ms. Irina Laurian[1,5], Ms Anna Dorfman[1,5], Ms. Efrat Chorna[1,6], Dr. Asaf Oren[1,2], Dr. Ori Eyal[1,2], Dr Avivit Brener[1,2], Prof. Yael Lebenthal[1,2]

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[2]Tel Aviv University, Faculty of Medicine, Tel Aviv, Israel
[3]Tel Aviv University, Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv, Israel
[4]Tel Aviv Sourasky Medical Center, The Nutrition & Dietetics Unit, Tel Aviv, Israel
[5]"Dana-Dwek" Children's Hospital, Tel Aviv Sourasky Medical Center, Nursing Services, Tel Aviv, Israel
[6]Tel Aviv Sourasky Medical Center, Social Services, Tel Aviv, Israel

09:27-09:39 **Familial Resemblance for Body Mass Index at Age 17: A National Intergenerational Cohort Analysis**

Dr. Maya Simchoni[1], Prof. Gabriel chodick[2], Mrs. Britt Wang Jensen[3], Mrs. Estela Derazne[4], Prof. Orit Pinhas-Hamiel[4,5], Dr. Regev Landau[1], Dr. Alon Abramovich[1], Prof. Arnon Afek[4,6], Prof. Jennifer Lyn Baker[3], Prof. Gilad Twig[4,7,8]

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[3]Center for Clinical Research and Prevention, Copenhagen University Hospital-Bispebjerg and Frederiksberg, Denmark
[4]Tel Aviv University Faculty of Medicine, Israel
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[6]Central Management, Sheba Medical Center, Israel
[7]The Institute of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Israel
[8]The Gertner Institute for Epidemiology and Health Policy Research, Israel

08:15-09:45 **Parallel Sessions**
Abstracts: Bone and Thyroid

Hall B

Chairs: **Dr. Pinchas Klien**, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center
Dr. Galia Gat-Yablonski, Schneider Children's Medical Center

08:15-08:27 **The Incidence of Fractures in Cancer Patients Initiating Immune Check-Point Inhibitors**

Ruti Karov[1], Dr. Eugene Feigin[1], Dr. Esther Osher[1], Prof. Yona Greenman[1], Dr. Vanessa Rouach[1]

[1]Institute of Endocrinology diabetes hypertension and metabolism, Tel-Aviv Souraski Medical Center

08:27-08:39 **Fracture risk among children and adolescents with diabetes mellitus: a nationwide cohort study**

Dr. Galia Zacay[1,2], Ms. Hagit Gabay[1], Dr. Liana Tripto-Shkolnik[1,2,3], Dr. Noah Gruber[2,4], Prof. Dalit Modan-Moses[1,2,4], **Yael Levy-Shraga**[1,2,4]

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[2]Sackler School of Medicine, Tel Aviv University, Israel
[3]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Israel
[4]Pediatric Endocrinology and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Israel

08:39-08:51 **Outcomes in Maternal Graves' Disease: A Population-Based Mother-Infant Dyad Cohort Study**

Eyal Cohen-Sela[1,2], Dr. Avivit Brener[1,2], Dr. Orian Raviv[1,2], PhD Michal Yackobovitch-Gavan[3], PhD Shlomo Almashanu[4], Prof. Ronella Marom[2,5], Dr. Matan Anteby[2,6], Prof. Liran Hiersch[2,6], Prof. Yael Lebenthal[1,2]

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[3]Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]The National Newborn Screening Program, Ministry of Health, Tel-Hashomer, Israel
[5]Department of Neonatology, Lis Maternity and Women's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[6]Department of Obstetrics and Gynecology, Lis Maternity and Women's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

08:51-09:03 **Surgery for Papillary Thyroid Carcinoma with Minimal Extra-Thyroid Extension – Is Lobectomy Enough?**

Dr. Anner Moskovitz[1], Dr. Nir Tsur[1], Dr. Keren Kaminer[2], Dr. Dean Dudkiewicz[1], Prof. Eyal Robenshtok[2,3]

[1]Otorhinolaryngology-Head and Neck Surgery, Rabin Medical Center, Israel
[2]Endocrinology, Rabin Medical Center, Israel
[3]Faculty of Medicine, Tel Aviv University, Israel

09:03-09:15 **Impact of Anti-Osteoporosis Medications on the Risk of Recurrent Hip Fracture**

Dmitry Shklovsky[1], Mr. Itay Pansky[2], Dr. Uri Yoel[1,3], Dr. Ran Abuhasira[2,3], Dr. Merav Fraenkel[1,3]

[1]Endocrine unit, Soroka University Medical Center, Beer Sheva, Israel
[2]Clinical Research Center, Soroka University Medical Center, Beer Sheva, Israel
[3]Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

09:15-09:27 **Is Parity a Risk Factor for Differentiated Thyroid Carcinoma? A Population-Based Case-Control Study**

M.D. Student Rotem Dan[1], Dr. Nuphar Vinegrad[2,3], Dr. Merav Fraenkel[2,3], Dr. Uri Yoel[2,3]

[1]The Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel
[2]Endocrinology, Soroka University Medical Center, Israel
[3]Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

09:27-09:39 **Denosumab is Associated with Decreased Mortality Compared to Zoledronic Acid in Diabetic Osteoporotic Patients: A Population-Based Cohort Study**

Dr. Vanessa Rouach[1,2], Dr. Hillary Gortler[3], Prof. Yona Greenman[1,3], Prof Gabriel Chodick[2], Dr. Inbal Goldshtein[4]

[1]Sourasky Medical Center, Tel Aviv, Institute of Endocrinology, Diabetes, Hypertension and Metabolism, Israel
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[3]Medical school, Sackler Faculty of Medicine, Tel Aviv University, Israel
[4]KI Research Institute, Israel

08:15-09:45 **Parallel Sessions**
Abstracts: Type 1 Diabetes
Hall C

Chairs: **Prof. Orit Hamiel**, Head of Pediatric and Diabetes Unit, Edmond and Lilly Safra Children's Hospital, Sheba Medical Center
Prof. Yuval Dor, Department of Developmental Biology and Cancer Research, The Institute for Medical Research Israel-Canada, The Hebrew University-Hadassah Medical School

08:15-08:27 **Disrupted RNA Editing in Beta Cells Mimics Early-Stage Type 1 Diabetes**

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

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[3]The Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Israel
[4]Department of Endocrinology and Metabolism, The Hebrew University of Jerusalem, Israel

08:27-08:39 **G6PC2 Controls Glucagon Secretion by Defining the Setpoint for Glucose in Pancreatic Alpha-Cells**

Reut Rifkind[1,2], Dr. Varun Bahl[3,4], Mr. Eric Waite[3,4], Ms. Zenab Hamdan[1,2], Dr. Catherine Lee May[3,4], Dr. Elisabetta Manduchi[3,4], Prof. Benjamin F. Voight[3,4,5], Dr. Michelle Y.Y. Lee[3,4], Mr. Mark Tigue[3,4], Prof. Nicholas Manuto[3,4], Prof. Benjamin Glaser[2], Dr. Dana Avrahami[1,2], Prof. Klaus H. Kaestner[3,4]

[1]Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel
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[3]Institute of Diabetes, Obesity, and Metabolism, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, PA, USA
[4]Department of Genetics, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, PA, USA
[5]Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, PA, USA

08:39-08:51 **To Count or not to Count? Simplified Carbohydrate Estimation Superior to Precise Counting with AHCL**

Noga Minsky[1], Dr. Roy Shalit[1], Mr. Andrea Benedetti[2], Ms. Maya Laron-Hirsh[1], Prof. Ohad Cohen[1,2,3], Dr. Natalie Kurtz[2], Dr. Anirban Roy[2], Dr. Benyamin Grosman[2], Prof. Amir Tirosh[1,3]

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[2]Medtronic, Northridge, California, USA
[3]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

08:51-09:03 **Inhibition of Somatostatin Secretion Promotes Complete Remission of Diabetes in Mice**

Ms. Yara Hamshawi, **Ron Piran**[1]
The Azrieli Faculty of Medicine, Bar-Ilan University, Israel

09:03-09:15 **Analysis of Type 1 Diabetes Trends in Israel**

Hadar Duskin-Bitan[1,2,3], Prof Amir Tirosh[4,5], Prof. Walid Saliba[6], Mr. Udi Altman[6], Mrs. Tanya Beckenstein[3], Prof. Doron Netzer[3], Dr. Shlomit Yaron[3], Prof. Arnon D Cohen[3], Dr. Ronen Arbel[3,7], Prof. Ilan Shimon[1,8], Dr. Alon Peretz[3,9]

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[2]Sackler School of Medicine, Tel Aviv Univercity, Israel
[3]Community Medical Services Division, Clalit Health Services, Israel
[4]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Israel
[5]Sackler School of Medicine, Tel Aviv Univercity, Sackler School of Medicine
[6]Department of Community Medicine and Epidemiology, Carmel Medical center, Israel
[7]Sapir College, Israel
[8]Sackler School of Medicine, Tel-Aviv University, Israel
[9]School of Public Health, University of Haifa, Israel

09:15-09:27 **Precision Diabetes: Identification and Characterization of Monogenic Diabetes in a Tertiary Pediatric Diabetes Center in Israel**

Idan Yoel[1,2], Dr. Martine Vaxillaire[3,4], Dr. Eve Stern[1,2], Dr. Mehdi Derhourhi[3,4], Prof. Philippe Froguel[3,4,5], Prof. Yael Levy-Shraga[1,2], Prof. Dalit Modan-Moses[1,2], Dr. Amélie Bonnefond[3,4,5], Prof. Orit Pinhas-Hamiel[1,2], Dr. Noah Gruber[1,2]

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[2]School of Medicine, Tel-Aviv University, Israel
[3]Inserm UMR1283, CNRS UMR8199, European Genomic Institute for Diabetes (EGID), Institut Pasteur de Lille, Lille University Hospital, France
[4]Université de Lille, France
[5]Department of Metabolism, Imperial College London, England

09:27-09:39 **ADIR- the Antibody Detection Israeli Research not for Children Only**
Dr. Tal Oron, 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

09:45-10:15 **Refreshments & Visit at the Exhibition**

10:15-11:30 **Opening Session: Innovative Endocrinology 2024**

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Hall A

Chairs: **Prof. Gil Leibowitz**, President of the Israel Endocrine Society (IES),The Hadassah Diabetes Unit, Director. Department of Endocrinology, Hadassah Medical Center, Jerusalem
Prof. Amir Tirosh, Director, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center; Professor of Medicine, Tel-Aviv University School of Medicine

10:15-10:25 **Greetings**

10:25-10:35 **Grants Summary**

10:35-11:20 **New Evidence in Cardiometabolic Medicine: What Can We SELECT Now?**
Prof. Daniel Drucker, Mt. Sinai Hospital, Lunenfeld Tanenbaum Research Institute University of Toronto

11:20-11:30 **Discussion**

11:30-11:50 **Refreshments & Visit at the Exhibition**

11:50-13:30	**Parallel Sessions** **Male Hypogonadism, Spermatogenesis & Cardio-Metabolic Disease**	Hall A
	Chairs: **Prof. Yona Greenman**, Director, Institute of Endocrinology and Metabolism Tel Aviv-Sourasky Medical Center, Faculty of Medicine, Tel Aviv University **Dr. Yoel Toledano**, Division of Maternal Fetal Medicine, Rabin Medical Center; Medical Division, Meuhedet	
11:50-12:20	**Hypogonadism, Testosterone Replacement Therapy & CV Risk: How can we TRAVERSE it?** **Prof. Giovanni Corona**, Maggiore-Bologna Hospital, Bologna, Italy	
12:20-12:45	**Towards a "Testis in a Dish"- An in Vitro Model of the Testis** **Dr. Nitzan Gonen**, Life Sciences Faculty, Bar-Ilan University	
12:45-13:30	**Obesity & Male Infertility/Hypogonadism: A Gordian Knot?** **Prof. Giovanni Corona**, Maggiore-Bologna Hospital, Bologna, Italy	
11:50-13:30	**Type 1 Diabetes: The Role of Immunology in Pathophysiology & Prevention**	Hall B
	Chairs: **Prof. Gil Leibowitz**, President of the Israel Endocrine Society (IES),The Hadassah Diabetes Unit, Director. Department of Endocrinology, Hadassah Medical Center, Jerusalem **Prof. Michael D. Walker**, Dept. of Biomolecular Sciences, Weizmann Institute of Science, Rehovot	
11:50-12:30	**The Key Role for Interferons in the Dialogue Between Beta Cells and the Immune System in Type 1 Diabetes** **Prof. Decio L. Eizirik**, The ULB Center for Diabetes Research, Medical Faculty, Universite Libre de Bruxelles	
12:30-13:00	**Disrupted RNA Editing as a Path to Type 1 Diabetes** **Prof. Yuval Dor**, Hebrew University-Hadassah Medical School	
13:00-13:20	**Prevention of Type 1 Diabetes 2024: What's New?** **Prof. Amir Tirosh**, Director, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center; Professor of Medicine, Tel-Aviv University School of Medicine	
13:20-13:30	**Discussion**	
13:30-14:20	**Lunch and & Visit the Exhibition**	
14:20-16:00	**Parallel Sessions** **Transition from Childhood to Adulthood in Endocrine Disorders:** In Memory of **Prof. Zeev Hochberg**	Hall A
	Chairs: **Dr. Michal Gershinsky**, Department of Endocrinology and Diabetes Linn Medical Center, Clalit Health Services, Haifa; Carmel Medical Center, Haifa; Technion - Israel Institute of Technology **Dr. Tal Ben-Ari Sekel**, Head of the Pediatric Endocrinology and Diabetes Unit, Sylvan Adam Children's Hospital, Edith Wolfson Medical Center	
14:20-14:35	**Finding Happiness and Meaning as an Endocrinologist** **Dr. Irit Hochberg**, Head of Diabetes Service, Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus. Chair of Endocrinology, Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa	
14:35-14:55	**Growth Hormone Replacement Therapy: From Childhood to Adulthood** **Prof. Yael Lebenthal**, Director, the Institute of Pediatric Endocrinology, Diabetes and Metabolism, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center	
14:55-15:15	**Hypophosphatemic Rickets - The Never-Ending Story** **Dr. Shelly Levi**, Schneider Children's Medical Center of Israel	Sponsored by: MEDISON
15:15-15:35	**The Transition of Youth with Type 1 Diabetes to the Adult World: Why & How Should it Truly Be?** **Prof. Marianna Rachmiel**, Head Pediatric and Diabetes Institute Shamir (Assaf Haroffeh) Medical Center	
15:35-15:50	**Current and Emerging Therapies for Achondroplasia: The Dawn of a New Era** **Dr. Ravit Regev**, Pediatric Bone Metabolism Disorders, Pediatric Endocrinology, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center	Sponsored by: MEDISON
15:50-16:00	**Discussion**	

14:20-16:00	**Diabetes Complications: State of the Art 2024**	Hall B
	Chairs: **Dr. Liat Barzilay Yoseph**, Endocrine institute, Meir medical center **Dr. Amir Bashkin**, Director of the endocrinology and diabetes unit, Galilee Medical Center	
14:20-14:40	**Diabetic Retinopathy - What's New?** **Dr. Alik Rosenfeld**, Ophthalmologist, Retina Specialist, Retina and Cataract Surgeon, WMC	Sponsored by: Roche Without Program Input
14:40-15:05	**The Year in Endo-Nephrology: Updates from the International Nephrology Conferences** **Dr. Nomy Levin-Iaina**, Head Department of Nephrology and Hypertension Barzilai University Medical Center	
15:05-15:25	**Unraveling the Heart in Diabetes: What can we Learn from the ECHO?** **Dr. Nir Flint**, Senior Cardiologist, Tel Aviv Sourasky Medical Center	Sponsored by: Boehringer Ingelheim
15:25-15:50	**The Liver & The Heart - An Intimate Relationship** **Prof. Hilla Knobler**, Diabetes Institute, Meuhedet HMO. Faculty of Medicine, Hebrew University	
15:50-16:00	**Discussion**	
16:00-16:20	**Refreshments & Visit at the Exhibition**	
16:20-17:40	**Parallel Sessions** **Diabesity: Twin Non-Communicable Epidemics**	Hall A
	Chairs: **Dr. Ido Goldstein**, Institute of Biochemistry, Food Science and Nutrition, The Robert H. Smith Faculty of Agriculture, Food and Environment The Hebrew University of Jerusalem **Dr. Elena Izkhakov**, Director of Endocrine Clinics, Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center	
16:20-16:50	**Overcoming Obesity - The Discovery of Multi Receptor Drugs** (Recorded Lecture) **Prof. Matthias Tschöp**, Helmholtz Munich	
16:50-17:15	**Weight Cycling in Obesity: A Common Condition with Unclear Health Impact** **Prof. Assaf Rudich**, Clinical Biochemistry and Pharmacology Department, Faculty of Health Sciences, Ben-Gurion University	
17:15-17:30	**The "Twin/Triplet" Agonists for Diabetes Treatment** **Dr. Roy Eldor**, Director, Diabetes Unit, Institute of Endocrinology, Metabolism & Hypertension, Tel-Aviv Sourasky Medical Center, Tel-Aviv	
17:30-17:40	**Discussion**	
16:20-17:40	**Metabolic Bone Disease: Bench to Bed**	Hall B
	Chairs: **Dr. Merav Fraenkel**, Head of Endocrine Unit, Soroka University Medical Center **Dr. Vanessa Rouach**, Bone Diseases Unit, Head; Institute of Endocrinology, Diabetes and Metabolism, Tel aviv Sourasky Medical Center	
16:20-16:45	**WhatsApp with the Bones? Breaking News from a Real-World Virtual Platform** **Dr. Gloria Tsvetov**, Endocrine Institute, Rabin Medical Center	
16:45-17:15	**Optimizing Bone Strength: Insights into Osteoanabolic Therapy for Osteoporosis** (Recorded Lecture with Live Q&A) **Prof. Bente L Langdahl**, Dept of Endocrinology, Aarhus University Hospital and Dept of Clinical Medicine, Aarhus University	Sponsored by the Medical Department of: MEDISON
17:15-17:30	**Metabolic Bone Disease: Insights from the Rehabilitation World** **Dr. Michael Bahar**, Director, Physical Medicine and Rehabilitation Unit, Rabin medical Center, Beilinson Hospital, Petach-Tikva	Sponsored by: Dexcel pharma
17:30-17:40	**Discussion**	

Tuesday, April 2nd

07:30-08:15 **Registration, Refreshments & Visit the Exhibition**

Morning Meditation

08:15-09:45 **Parallel Sessions**
Abstracts: Neuroendocrinology
Hall A

Chairs: **Prof. Simona Glasberg**, Director, Neuroendocrine Tumor Unit, ENETS Center of Excellence, Consultant, Endocrinology & Internal Medicine; Division of Internal Medicine Hadassah Medical Center and Faculty of Medicine, The Hebrew University of Jerusalem
Prof. Philippa Melamed, Technion-Israel Institute of Technology

08:15-08:27 **Changes in DNA Methylation Patterns Linearly Associated with DHEAS Levels in Prepubertal Children are Found Near Puberty-Related Genes**

Maya Sudman[1], Prof. Gillian Bentley[2], Assoc. Prof. Reinhard Stöger[3], Prof. Philippa Melamed[1]

[1]Faculty of Biology, Technion - Israel Institute of Technology, Haifa, Israel
[2]Department of Anthropology, Durham University, Durham, UK
[3]School of Biosciences, University of Nottingham, Nottingham, UK

08:27-08:39 **Endogenous Cushing's Syndrome and Cancer Risk: A Nationwide Israeli Cohort Study**

Yaron Rudman[1], Prof. Maria Fleseriu[2], BSc Laura Dery[3], Dr. Hiba Masri-Iraqi[1], Dr Liat Sasson[1], MSc Tzippy Shochat[4], BSc Shiri Kushnir[5], Prof. Ilan Shimon[1], Prof. Amit Akirov[1]

[1]Institute of Endocrinology, Beilinson Hospital, Rabin Medical Center, Israel
[2]Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science University, Portland, OR, USA
[3]Faculty of Medicine, Tel Aviv University, Israel
[4]Biostatistics Unit, Beilinson Hospital, Rabin Medical Center, Israel
[5]Research Authority, Beilinson Hospital, Rabin Medical Center, Israel

08:39-08:51 **The Role of Suprachiasmatic VIP Neurons in Circadian Rhythm Regulation of the Estrous Cycle in Female Mice**

Dr. Anat Kahan[1], Mr. Gerard M. Coughlin[2], Dr. Máté Borsos[2], Ms. Nikhila P. Swarna[2], Prof. Bingni W. Brunton[3], Prof. Viviana Gradinaru[2]

[1]Animal Sciences, The Hebrew University, Israel
[2]Division of Biology and Biological Engineering, California Institute of Technology, CA, USA
[3]Department of Biology, University of Washington, WA. USA

08:51-09:03 **Visual Morbidity in Macroprolactinoma: a Retrospective Cohort Study**

Yaron Rudman[1], Dr. Hadar Duskin-Bitan[1], Dr. Hiba Masri-Iraqi[1], Prof. Amit Akirov[1], Prof. Ilan Shimon[1]

[1]Institute of Endocrinology, Rabin Medical Center, Beilinson Hospital, Israel

09:03-09:15 **Single-Cell and Experimental Analyses Indicate Pathways of Transcription Factor-Driven Dierentiation of Post-Natal Pituitary Stem Cell to Gonadotropes**

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

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

09:15-09:27 **Unraveling the Homeostasis of Gastric Neuroendocrine Cells: Insights from Single-Cell RNA Sequencing, Transgenic Mouse Models and Human Organoids**

Amit Elad[1], Dr. Rachel Schyr[1], Mrs. Haya Ben-Hayun[1], Mrs. Deborah Durand[2], Mrs. Michelle Malis[1], Mr. Mohamed Abo-Tanha[1], Mr. Doron Kleiman[1], Mr. Botros Moalem[1], Mr. Moshe Pashkus[1], Mrs. Tamar Harats[1], Mrs. Dana Sender[1], Mrs. Dana Orzech[1], Dr. Sharona Tornorvski[3], Dr. Shira Anzi[1], Dr. Yael Riahi[4], Dr. Ariel Benson[5], Dr. Ronit Grinbaum[6], Dr. Esther Forkosh[5], Dr. Yuval Yishai[5], Dr. Liron Birimberg-Schwartz[2], Dr. Myriam Grunewald[2], Prof. Danny Ben-Zvi[1]

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[3]Faculty of Medicine, Department of Immunology and Cancer Research, Hebrew University of Jerusalem, Israel
[4]Endocrinology and Metabolism service, Hadassah-Hebrew University Medical Center, Israel
[5]Institute of Gastroenterology and Liver Diseases, Department of Internal Medicine, Hadassah-Hebrew University Medical Center, Israel
[6]Department of Surgery, Hadassah-Hebrew University Medical Center Mount Scopus, Israel

09:27-09:39 **Extensive Elimination of Acinar Cells During Normal Postnatal Pancreas Growth**

Dr. Miri Stolovich-Rain[1], Dr. Ori Fridlich[1], Dr. Shira Azulai[1], Dr. Agnes Klochendler[1], Dr. Shira Anzi[1], Dr. Judith Magenheim[1], Dr. Ilan Stein[2,3], Mss. Fatima Mushasha[2], Benjamin Glaser[4], Eli Pikarsky[2,3], Danny Ben-Zvi[1], Yuval Dor[1]

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[3]Department of Pathology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[4]Endocrinology and Metabolism Service, Department of Internal Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

08:15-09:45 Parallel Sessions
Abstracts: Pregnancy, Reproduction and Growth

Hall B

Chairs: **Dr. Orit Berenholtz Goultschin**, Shaare Zedek Medical Center, Meuhedet
Dr. Eran Gershon, Agricultural Research Organization

08:15-08:27 **Gestational Diabetes in Multiple Pregnancies and Risk for Type 2 Diabetes Mellitus - A 5-Year Cohort Study**

Amir Naeh[1], Dr. Esther Maor-Sagie[1,2], Prof. Mordechai Hallak[1,2], Dr. Yoel Toledano[2,3], Prof. Rinat Gabbay-Benziv[1]

[1]Department of Obstetrics and Gynecology, Hillel Yaffe Medical Center
[2]Meuhedet HMO
[3]Endocrinology Clinic, Division of Maternal Fetal Medicine, Helen Schneider, Women's Hospital, Rabin Medical Center

08:27-08:39 **First-Trimester Fasting Plasma Glucose Levels and Progression to Type 2 Diabetes: A 5-Year Cohort Study**

Dr. Esther Maor-Sagie[1,2,3], Prof. Mordechai Hallak[1,2,3], Dr. Yoel Toledano[3], Prof. Gilad Twig[4], Prof. Rinat Gabbay-Benziv[1,2]

[1]Department of Obstetrics and Gynecology, Hillel Yaffe Medical Center, Israel
[2]The Ruth and Bruce Rappaport Faculty of Medicine, Technion- Israel Institute of Technology, Israel
[3]Meuhedet HMO, Israel
[4]Institute of Endocrinology, Diabetes and Metabolism, The Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Israel

08:39-08:51 **Glucose Intolerance in Pregnancy and Risk of Early-Onset Type 2 Diabetes: A Population-Based Cohort Study**

Dr. Aya Bardugo, Dr. Cole Bendor, Dr. Maya Nitecki, Dr. Ran Rotem, Dr. Avishai Tsur, Prof. Hertzel Gerstein, Mrs. Dorit Tzur, Prof. Orit Pinhas-Hamiel, Prof. Tali Cukierman-Yaffe, Prof. Itamar Raz, Prof. Moshe Hod, Prof. Amir Tirosh, Prof. Yael Lebenthal, Prof. Arnon Afek, Prof. Gabriel Chodick, **Prof. Gilad Twig**

08:51-09:03 **A Distal Super-Enhancer of the FSHB Gene Coordinates Activity of the Locus and Shapes the Chromatin Landscape in a Mouse Model of Menopause**

Tal Refael[1], Dr. Lilach Pnueli[1], Ms. Gil Golan[1], Mrs. Maya Sudman[1], Mr. Sujay Y.Naik[2], Prof. Philippa Melamed[1]

[1]Faculty of Biology, Technion-Israel Institute of Technology, Haifa, Israel
[2]The Rappaport Faculty of Medicine and Research Institute, Technion-Israel Institute of Technology, Haifa, Israel

09:03-09:15 **Hot Flashes are Associated with Text-Based Markers of Cognitive Impairment: Observational Study of Posts on Social Media**

Dr. Sigal Shaklai[1,2], Dr. Merav Serebro[1], Prof. Yona Greenman[1,2], Prof. Elad Yom-Tov[3]

[1]Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center, Israel
[2]Sackler Faculty of Medicine, Tel-Aviv University, Israel
[3]Department of Computer Science, Bar-Ilan University, Israel

09:15-09:27 **Predicting Childhood Obesity from Maternal Thyroid-Related Parameters via Machine Learning**

Dr. Yaniv S. Ovadia[1], Prof. Natalya Bilenko[2,3], Dr. Dov Gefel[1], Mrs. Shani R. Rosen[4], Dr. Orit Mazza[5], Mrs. Yael Avrahami-Benyounes[6], Dr. Ludmila Groisman[7], Dr. Efrat Rorman[7], Dr. Tatiana Ketslakh[1], Dr. Shlomo Fytlovich[8], Prof. Eyal Y. Anteby[1,3], Dr. Simon Shenhav[1,3]

[1]Obstetrics and Gynecology Division, Barzilai University Medical Center, Ashkelon, Israel
[2]Medical Office of Southern District, Ministry of Health, Ashkelon, Israel
[3]Faculty of Health Sciences, Ben-Gurion University of Negev, Beersheba, Israel
[4]School of Nutritional Science; Institute of Biochemistry, Food Science and Nutrition; Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Rehovot, Israel
[5]Lowenstein Rehabilitation Medical Center, Clalit Health Services, Ra'anana, Israel
[6]Women's Health Center, Maccabi Healthcare Services, Southern Region, Beersheba, Israel
[7]National Public Health Laboratory, Ministry of Health, Tel Aviv, Israel
[8]Laboratory of Clinical Biochemistry, Barzilai University Medical Center, Ashkelon, Israel

09:27-09:39 **Evaluation of Serum Glycosylated Hemoglobin for Dysglycemia After Pregnancy Complicated by Gestational Diabetes Mellitus: A National Data Analysis**

Nadav Cohen[1,2], Dr. Yoel Toledano[3], Dr. May Shafir[1], Prof. Ofer Lavie[1], Dr. Reuven Keidar[1], Dr. Ariel Zilberlicht[1]

[1]Obstetrics and Gynecology, Carmel Lady Davis Medical Center, Haifa
[2]Rappaport Faculty of Medicine, Technion University, Haifa
[3]Division of Maternal Fetal Medicine, Helen Schneider Hospital for Women, Rabin Medical Center Petah Tikva

08:15-09:45 Parallel Sessions
Abstracts: T2D and metabolism

Hall C

Chairs: **Dr. Michal Kasher Meron**, Endocrinology, Meir Medical Center, Clalit Health Services; School of Medicine, Tel Aviv University
Dr. Taiba Zornitzki, M.D., Head of the Endocrinology and Diabetes Institute Kaplan Medical Center, Rehovot

08:15-08:27 **Fib-4 Score is a Prognostic Predictor of End-Stage Liver Disease: A Nationwide Retrospective Study**

Dr. Michal Kasher Meron[1,2], Dr. Tzipi Hornik-Lurie[3], Dr. Pnina Rotman-Pikielny[2,4], Dr. Gil Ben Yaakov[5], Dr. Gilad Twig[6,7,8,9], Dr. Tomas Karpati[10]

[1]Endocrinology, Meir Medical Center, Clalit Health Services, Israel
[2]School of Medicine, Tel Aviv University, Israel
[3]Research Department, Meir Medical Center, Clalit Health Services, Israel
[4]Endocrine Department, Meir Medical Center, Clalit Health Services, Israel
[5]Gastroenterology, Edith Wolfson Medical Center, Israel
[6]Department of Military Medicine, Hebrew University of Jerusalem Faculty of Medicine, Jerusalem, Israel

[7]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel Hashomer, Ramat Gan Israel
[8]Department of Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[9]The Gertner Institute for Epidemiology & Health Policy Research, Sheba Medical Center, Ramat Gan, Israel
[10]Faculty of Sciences, Holon Institute of Technologies, Israel

08:27-08:39 **Mid-Aged Mice Normalize Obesity-Induced Dysglycemia During Weight Loss Along with Aggravated Hypothalamic Inflammation: Implications to Mid-Age Weight Cycling and Neurodegenerative Disorders?**

Alon Zemer[1,2], PhD. Yulia Haim[1], PhD. Alexandra A. Tsitrina[3], Prof. Yair Pincu[4], MD Uri Yoel[5,6], BSc Habib Mualem[1], Prof. Alon Monsonego[2,7], Prof. Assaf Rudich[1]

[1]Department of Clinical Biochemistry, Faculty of Health Sciences, Ben Gurion University of the Negev, Israel
[2]The Shraga Segal Department of Microbiology, Immunology, and Genetics, Ben Gurion University of the Negev, Israel
[3]Ilse Katz Institute for Nanoscale Science and Technology, Ben Gurion University of the Negev, Israel
[4]Department of Health and Exercise Science, University of Oklahoma, OK, United States
[5]Endocrinology Diabetes and metabolism, Soroka University Medical Center, Israel
[6]Faculty of Health Science, Ben Gurion University of the Negev, Israel
[7]The National Institute of Biotechnology and Regenerative Medicine and Stem Cell Research Center, Ben Gurion University of the Negev, Israel

08:39-08:51 **Hepatocyte CB1 Receptor Regulation of Fatty Acid Oxidation and Steatosis: Metabolomics Insight**

Dr. Jie Liu, Ms. Anna Oliverio, **Radka Kocvarova**, Dr. Liad Hinden, Dr. Muhammad Arif, Dr. Abhishek Basu, Dr. Resat Cinar, Dr. Bin Gao, Prof. Joseph Tam, Dr. George Kunos

08:51-09:03 **Safety of SGLT2 Inhibitors in Kidney Transplant Recipients with Diabetes Mellitus**

Talia Diker Cohen[1,2], Dr. Amir Polansky[2,3], Dr. Idan Bergman[2,4], Dr. Gida Ayada[2,4], Dr. Tanya Babich[2,5], Prof. Amit Akirov[1,2], Dr. Tali Steinmetz[1,2], Dr. Idit Dotan[2,6]

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[2]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Clalit Health Services, Petah Tikva, Israel
[4]Internal Medicine C, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel
[5]Research Authority, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel
[6]Institute of Nephrology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

09:03-09:15 **Novel Regulatory Role of Kidney Proximal Tubular GLUT2 in Kidney and Systemic Energy Metabolism**

Dr. Liad Hinden[1] ,Dr. Majdoleen Ahmad[1], Dr. Anna Permyakova[1], Dr. Saja Baraghithy[1], Dr. Ifat Abramovich[2], Dr. Bella Agranovich[2], Dr. Ori Shalev[3], Dr. Aviram Kogot-Levin[6], Dr. Alina Nemirovski[1], Prof. Eyal Gottlieb[2], Dr. Rinat Abramovitch[4,5], Prof. Gil Leibowitz[6] and Prod. Joseph Tam[1]

[1]Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
[2]Laura and Isaac Perlmutter Metabolomics Center, B. Rappaport Faculty of Medicine, Technion-Israel Inst of Technology, Haifa, Israel
[3]Metabolomics Center, Core Research Facility, the Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
[4]The Wohl Institute for Translational Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[5]The Goldyne Savad Institute of Gene Therapy, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[6]Diabetes Unit and Endocrine Service, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

09:15-09:27 **SGLT2 Inhibitors Show Cardiovascular Benefit in Kidney Transplant Recipients with Diabetes Mellitus**

Dr. Idit Dotan[1,2], Dr. Amir Polansky[2,3], Dr. Idan Bergman[2,4], Dr. Gida Ayada[2,4], Dr. Tanya Babich[2,5], Prof. Amit Akirov[1,2], Dr. Tali Steinmetz[2,6], Talia Diker Cohen[1,2]

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[3]Clalit Health Services, Petah Tikva, Israel
[4]Internal Medicine C, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel
[5]Research Authority, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel
[6]Institute of Nephrology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

09:27-09:39 **Metabolic and Functional Factors Associated with a Change in Resting Metabolic Rate Among Older Adults with Type 2 Diabetes– Results from the CEV-65 Randomized Trial**

Assaf Buch[1,2], Prof. Yona Greenman[1], Dr. Sharon Barak[3,4], Dr. Roy Eldor[1]

[1]Endocrinology, Tel Aviv Medical Center, Israel
[2]Nutritional Sciences, Ariel University, Israel
[3]Pediatric Rehabilitation, The Chaim Sheba Medical Center, Israel
[4]Department of Nursing, Ariel University

09:45-10:15 **Refreshments & Visit at the Exhibition**

10:15-11:45 **Parallel Sessions**
Sarcopenia - A Target Organ of Aging & Diabetes — Hall A

Chairs: **Dr. Yoel Toledano**, Division of Maternal Fetal Medicine, Rabin Medical Center; Medical Division, Meuhedet
Prof. Tali Cukierman-Yaffe, The Center for Successful Aging with Diabetes, Division of Endocrinology and Metabolism, Sheba Medical Center; Department of Epidemiology, School of public health, Faculty of Medicine, Tel-Aviv University

10:15-10:45 **Defining and Measuring Sarcopenia in Older People with Diabetes**
Prof. Tali Cukierman-Yaffe, The Center for Successful aging with diabetes, division of Endocrinology and metabolism, Sheba medical Center; Department of Epidemiology, School of public health, Faculty of Medicine, Tel-Aviv University

10:45-11:05 **Senescent Cells in Aging and Age-Related Disease: The Good, the Bad and the Ugly**
Prof. Valery Krizhanovsky, Department of Molecular Cell Biology Weizmann Institute of Science, Rehovot

11:05-11:25 **Body Composition & Weight Loss Therapy: Present & Future**
Prof. Ofri Mosenzon, Adamical Director of the School of Continues Medical Education,Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem; Senior Medical Director, Regeneron Pharmaceuticals, Tarrytown< NY, USA

Sponsored By: REGENERON SCIENCE TO MEDICINE

11:25-11:45 **Physical & Nutritional Interventions to Prevent Sarcopenia**
Tal Yahalom-Peri, Sheba Medical Center, Division of Endocrinology, Epidemiology Department, School of Public Health, Faculty of Health, Tel Aviv University

10:15-11:45 **Lessons of Genetics for The Endocrinologist** — Hall B

Chairs: **Dr. Michal Yacobi Bach**, Genetics and Endocrine Institutes, Sourasky Medical Center, Tel Aviv
Dr. Noa Shefer Averbuch, 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; Recanati Genetic Institute, Rabin Medical Center, Beilinson Campus, Petach Tikva

10:15-10:40 **Genetic Testing in Endocrinology: For Whom, When, Why and Where?**
Dr. Michal Yacobi Bach
Dr. Noa Shefer Averbuch

10:40-11:05 **Congenital Adrenal Hyperplasia- Simplifying the Complicated**
Dr. Michal Yacobi Bach

11:05-11:25 **Fifty Shades of Monogenic Diabetes- Everything You Wanted to Know and Did Not Dare to Ask**
Dr. Noa Shefer Averbuch

11:25-11:45 **Monogenic Obesity: Bardet-Biedel Syndrome**
Dr. Yael Sofer, Head of Obesity Clinic, Department of Endocrinology, Metabolism and Hypertension, Ichilov Sourasky Medical Center, Tel Aviv

Sponsored by: MEDISON

11:45- 12:45 **Parallel Sessions - Posters**
Abstracts: Adrenal and Steroid Hormones

Hall A

Chairs: **Prof. Yoav Sharoni**, Clinical Biochemistry and Pharmacology Faculty of Health Sciences, Ben-Gurion University of the Negev
Dr. Yonit Marcus, Senior Endocrinologist, Institute of Endocrinology Metabolism and Hypertension, Tel Aviv Sourasky Medical Center

11:45-11:52 **Using Point of Care Rapid Cortisol Measurement During Adrenal Venous Sampling - a Single Center Clinical Experience**

Hadas Rabani, Dr. Robert Sachner, Dr. Sawsan Yosefia, Dr. Michal Yeiches, Dr. Limor Chen-Konak, Dr. Clara Henig, Dr. Balsam Dakwar, Dr. Anan Shalata, Dr. Katya Jovanovic, Dr. Ilana Rosenblat, Dr. Mohmamad Sheikh Ahmad, Dr. Leonard Saiegh

11:52-11:59 **Adrenocortical Carcinoma - A Tertiary Center`s Recent ~10-year Experience**

Dr. Esther Osher[1], Prof. Karen Tordjman[1], Dr. Yael Sofer[1], Prof. Naftali Stern[1], Prof. Joseph Klausner[2], Dr. Guy Lahat[2], Prof. Nir Lubezky[2], Dr. Yaakov Goykhman[2], Dr. Boaz Sagie[2], Dr. Ravit Geva[3], Dr. Asaf Aizic[4], Dr. Rivka Kessner[5], Prof. Ido Wolf[3], Prof. Yona Greenman[1]

[1]Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center and Faculty of Medicine, Tel-Aviv University, Israel
[2]Department of Surgery, Tel-Aviv Sourasky Medical Center and Faculty of Medicine, Tel-Aviv University, Israel
[3]Department of Oncology, Tel-Aviv Sourasky Medical Center and Faculty of Medicine, Tel-Aviv University
[4]Institute of Pathology, Tel-Aviv Sourasky Medical Center and Faculty of Medicine, Tel-Aviv University
[5]Department of Radiology, Tel-Aviv Sourasky Medical Center and Faculty of Medicine, Tel-Aviv University

11:59-12:06 **Cortisol Secretion in Obesity Revisited: Lower Basal Serum Free Cortisol with Diminished Cortisol Response to the Low Dose 1ug ACTH Challenge**

Yael Sofer[1,2], Dr. Esther Osher[1,2], Prof. Yona Greenman[1,2], Dr. Yonit Marcus[1,2], Dr. Galina Shenkderman[1,2], Ms. Yaffa Moshe[1], Dr. Sigal Shaklai[1], Dr. Mariana Yaron[1], Dr. Dror Cantrell[3], Dr. Merav Serebro[1], Dr. Rona Limor[1], Prof. Karen Tordjman[1], Prof. Naftali Stern[1]

[1]Department of Endocrinology, Metabolism and Hypertension, Tel Aviv MC, Isreal
[2]Faculty of Medicine, Tel Aviv University, Israel
[3]Department "C" of Internal Medicine, Shamir Medical Center, Sackler Medical School Tel Aviv University, Tzrifin, Isreal

12:06-12:13 **Possible Association Between Promoter Methylation Level of Genes Encoding Catecholamine Metabolizing Enzymes and Metanephrine Secretion in Pheochromocytoma and Paraganglioma**

Dr. Anna Kaplinsky[1,2], Reut Halperin[2,3], Dr. Gadi Shlomai[2,3,4], **Prof. Amit Tirosh**[2,3]

[1]Cancer Center, Sheba Medical Center, Israel
[2]Faculty of Medicine, Tel Aviv University, Israel
[3]Division of Endocrinology, diabetes and metabolism, Sheba Medical Center, Israel
[4]Medicine D Ward, Sheba Medical Center, Israel

12:13-12:20 **Germline DNA Methylation Analysis Reveals Distinct Alterations in a Large Cohort of Patients with Germline SDHB Pathogenic Variant**

Dr. Reut Halperin[1,2], Mr. Roi Horwitz[3], Dr Amna Jabarin[1], Prof. Amit Tirosh[1,2]

[1]Endocrinology, diabetes and metabolism, Sheba Medical Center, Israel
[2]Medicine, Tel Aviv University, Israel
[3]Medicine, Technion, Israel

12:20-12:27 **Impact of Etiology, Sex and Remission Status on Erythrocytic Profile in Patients with Cushing's Syndrome: A Large Population Database Study**

Laura Dery[1], Ms. Julia Stern[1], Dr. Ilan Shimon[1,2], Dr. Yaron Rudman[1,2], Ms. Shiri Kushnir[3], Ms. Tzipora Shochat[4], Dr. Maria Fleseriu[5], Prof. Amit Akirov[1,2]

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[3]Research Authority, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel
[4]Biostatistics Unit, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel
[5]Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science University, Portland, Oregon, USA

12:27-12:34 **Low Dose Sublingual Estradiol Decreases Protein S, Generating a Potentially Pro-Thrombotic State: Interim Results of a Controlled Prospective Pilot Study of Treatment-Naïve Trans Women**

Med. Stud. Shelly Bar On[1,2], Dr. Iris Yaish[1], Dr. Merav Barzilai[2,3], Prof. Yona Greenman[1,2], Med. Stud. Guy Gindis[1,2], RN, BSc Yaffa Moshe[1], **Karen Tordjman**[1,2]

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[2]Faculty of Medicine, Tel Aviv University, Israel
[3]Institute of Hematology, Rabin Medical Center, Campus Beilinson, Israel

12:34-12:41 **The Estrogen Receptors and ARE/Nrf2 are Involved in Protecting Human Dermal Fibroblasts from Damage Caused by Mitochondrial Disfunction**

Aya Darawsha[1], Prof. Yoav Sharoni[1]
[1]Clinical Biochemistry and Pharmacology, Ben Gurion University, Israel

11:45- 12:45 Parallel Sessions -Posters Abstracts: Diabetes and obesity — Hall B

Chairs: **Dr. Kfir Sharabi**, Institute of Biochemistry, Food Science and Nutrition, The Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem
Dr. Rosane Ness Abramof, Clalit Health Services

11:45-11:52 **Predicting Factors for Adverse Outcomes of Acute Decompensated Heart Failure in Diabetic Patients Hospitalized in Internal Medicine Department**

Alena Kirzhner[1,2], Dr. Hefziba Green[1,2], Dr. Ronit Koren[3,4], Dr. Haitham abu Khadija[2,5], Ms. Danielle Sapojnik[2,6], Dr. Tal Schiller[2,7]

[1]Department of Internal Medicine A, Kaplan Medical Center, Israel
[2]Faculty of Medicine, Hebrew University of Jerusalem, Israel
[3]Department of Internal Medicine A, Yitzhak Shamir Medical Center, Zerifin, Israel
[4]Faculty of Medicine,, Tel Aviv University, Tel Aviv, Israel
[5]Department of Cardiology, Kaplan Medical Center, Israel
[6]Department of Clinical Nutrition, Kaplan Medical Center, Israel
[7]Department of Diabetes, Endocrinology and Metabolism, Kaplan Medical Center, Israel

11:52-11:59 **Unraveling the Metabolic and Endurance Effects of Novel PPAR-δ Agonists in Mice: Implications for Therapeutic Strategies in Metabolic Disorders**

Ameer Shufani[1], Prof. Joseph Tam, Prof. Michal Horowitz, Prof. Amiram Goldblum, Dr. Saja Baraghithy

[1]The Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Israel

11:59-12:06 **Timing of Gestational Diabetes Diagnosis and Progression to Type 2 Diabetes: A Comparative Analysis**

Dr. Esther Maor-Sagie[1,2,3], Prof. Mordechai Hallak[1,2,3], Dr. Amir Naeh[1,2], Dr. Yoel Toledano[3], Prof. Rinat Gabbay-Benziv[1,2]

[1]Department of Obstetrics and Gynecology, Hillel Yaffe Medical Center, Israel
[2]The Ruth and Bruce Rappaport Faculty of Medicine, Technion- Israel Institute of Technology, Israel
[3]Meuhedet HMO, Israel

12:06-12:13 **Characterization of Beta Senescence During Aging in Diabetes**

Dr. Nathalie Groen[1], Ms.C Eseye Feleke[2], Bs.C Mati Mesenyashin[2], Bs.C Adi Mazouz[2], Bs.C Reut Rifkind[2], Dr. Elisabetta Manduchi[3], Prof. Alexander van Oudenaarden[4], Prof. Eelco J. P. de Koning[5], Prof. Françoise Carlotti[5], Prof. Benjamin Glaser[6], Prof. Klaus H. Kaestner[3], **Dr. Dana Avrahami**[7]

[1]Department of Internal Medicine, Leiden University Medical Center, 2333 ZA Leiden,, Netherlands
[2]Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

[3]Departments of Genetics, and Institute for Diabetes, Obesity, and Metabolism, University of Pennsylvania, Philadelphia USA
[4]Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences (KNAW) and University Medical Center Utrecht, Utrecht, Netherlands
[5]Department of Internal Medicine, Leiden University Medical Center, 2333 ZA Leiden, Netherlands
[6]Department of Endocrinology and Metabolism, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[7]Department of Developmental Biology and Cancer Researc, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

12:13-12:20 **Senolytics Dasatinib and Quercetin Alleviate TypeI Diabetes-Related Cardiac Fibrosis in AKITA Mice**

Ghadeer Zatarah[1], Dr. Pushkar Shivam[1], Dr. Joshua Stokar[1], Dr. Irina Gurt[1], Prof. Rivka Dresner-Pollak[1]

[1]Endocrinology and Metabolism, Hadassah-Hebrew University Medical Center, Israel

12:20-12:27 **The Relationship Between Nutrition Knowledge and Dietary Adherence among Adults with Type 2 Diabetes**

Dr. Michal Kasher Meron[1,2], Dr. Adi Givati[3], Dr. Liat Barzilai-Yosef[1], Dr. Sophia Shapira[1], Dr. Erez Ramati[4], Dr. Nuha Younis Zeidan[3], Dr. Vered Kaufman-Shriki[5], Dr. Ofra Kalter-Leibovici[6,7], Dr. Pnina Rotman-Pikielny[1,2]
[1]Endocrinology, Meir Medical Center, Israel
[2]School of Medicine, Tel Aviv University, Israel
[3]Clalit Health Services, Israel
[4]Meuhedet, Israel
[5]Department of Nutrition Sciences, Ariel University
[6]Gertner Institute of Epidemiology and Health Policy Research, Tel-Hashomer
[7]Faculty of Medicine & Health Sciences, Tel-Aviv University

12:27-12:34 **Changes in Emotional and Uncontrolled Eating Induced by GLP1a Associated with Weight Loss, Weight Regain and Drug Cessation**

Noga Minsky[1], Ms. Sara Kutzel[2], Dr. Orly Tamir[3], Dr. Gabriella Segal-Lieberman[1]

[1]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel Hashomer, Israel
[2]Arrow Program for Medical Rsearch Education, Sheba Medical Center, Tel Hashomer, Israel
[3]The Pesach Segal Israeli Center for Diabetes Research and Policy in Diabetes, Sheba Medical Center, Tel Hashomer, Israel

12:34-12:41 **Hyperinsulinemia and the Insulin Secretion Threshold**

Doron Kleiman[1,2], Msc Sarah Knapp[1,2], Phd Rachel Ben-Haroush Schyr[1,2], Prof Danny Ben-Zvi[1,2]

[1]Developmental Biology and Cancer research, The Institute of Medical Research Israel-Canada, The Hebrew University of Jerusalem-Hadassah Medical School
[2]The Hebrew University Computational Medicine Center, The Hebrew University of Jerusalem

11:45- 12:45 Parallel Sessions - Posters Abstracts: Diabetes — Hall C

Chairs: **Dr. Hofit Cohen**, Lipid service director, The Bert W. Strassburger Lipid Center Sheba Medical Center, Tel-Hashomer
Dr. Ronny Helman, The Hebrew University of Jerusalem; Institute of Biochemistry, Food Science and Nutrition

11:45-11:52 **Mechanisms of Aldolase B Mediated Beta Cell Glucotoxicity**

Adi Mazouz[1,2], Dr. Judith Furth-Lavi[1,2], Dr. Sharona Tornovsky-Babeay[1,2], Ms. Reut Rifkind[1,2], Ms. Tamar Cohen[1,2], Ms. Eseye Feleke[1], Dr. Dana Avrahami[1,2], Prof. 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

11:52-11:59 **The Relationship Between Neonatal Hypoglycemia and Glucose Control During Labor of Mothers with Type 1 Diabetes**

Amna Jabarin[1], Dr. Rakefet Yoeli-Ullman[2,3], Mrs. Keren Levi[1], Dr. Nirit Agay[4], Dr. Ronen Fluss[5], Mrs. Arnona Ziv[4], Prof. Tali Cukierman-Yaffe[1,3,6]

[1]Division of Endocrinology, Diabetes and Metabolism, The Chaim Sheba Medical Center, Tel Hashomer, Israel
[2]Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel
[3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Gertner Institute, Sheba Medical Center, Tel Hashomer, Israel
[5]Biostatistics Unit, Gertner Institute, Sheba Medical Center, Tel Hashomer, Israel
[6]Epidemiology Department, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

11:59-12:06 **ER Stress-Induced Neonatal Diabetes: Effects of Glucotoxicity on β-Cell Function and Diabetes**

Elisheva Zemelman[1], Dr. Aviram Kogot-Levin, Dr. Yael Riahi, Professor Gil Leibowitz

[1]Endocrinology Department, Hadassah Medical Center of the Hebrew University of Jerusalem, IL

12:06-12:13 **Research Portal for Single-Cell RNA Atlas of Human Pancreatic Islets**

Haya Benhayon[1,2], Dr. Rachel Ben-Haroush Schyr[1,2], Prof Danny Ben-Zvi[1,2]

[1]Developmental Biology and Cancer research, The Institute of Medical Research Israel-Canada, The Hebrew University of Jerusalem-Hadassah Medical School, Jerusalem Israel
[2]The Hebrew University Computational Medicine Center, The Hebrew University of Jerusalem, Jerusalem Israel

12:13-12:20 **The Impact of Meal Bolus Timing on Postprandial Glucose Control with AHCL System: A Prospective Repeated Measure Study**

Maya Laron Hirsh[1], Prof. Amir Tirosh[1], Mrs. Shiran Shalem[1], Prof. Ohad Cohen[2], Dr. Benyamin Grossman[2], Mrs. Natalie Kurtz[2], Mr. Andrea Benedetti[2], Dr. Roy Anirban[2]

[1]Endocrinology, Sheba Medical Center, Israel
[2]Medtronic, Northridge, California

12:20-12:27 **Virtual reality`s Impact on Children with Type 1 Diabetes: A Randomized Cross-Over Trial on Anxiety, Pain, Adherence, and Glycemic Control**

Noah Gruber[1,2], Ms. Moran Shemesh-Iron[1], Dr. Ethel Kraft[1,2], Ms. Karen Mitelberg[1], Ms. Elinor Mauda[1], Dr. Michal Ben-Ami[1,2], Dr. Kineret Mazor-Aronovitch[1,2], Prof. Yael Levy-Shraga[1,2], Dr. Neriya Levran[1,2], Ms. Noah Levek[1], Prof. Eyal Zimlichman[2,3], Prof. Orit Pinhas-Hamiel[1,2]

[1]Pediatric Endocrine and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Israel
[2]School of Medicine, Tel-Aviv University, Israel
[3]Innovation and Transformation Management, Sheba Medical Center, Israel

12:27-12:34 **Characterizing Movement Patterns of Older Individuals with Type 2 Diabetes in Free-Living Environments Using Wearable Accelerometers**

Tal Yahalom-Peri[1,2], Dr. Veronika Bogina[3,4], Mrs. Yamit Basson-Shleymovich[2,5], Dr. Michal Azmon[1,6], Prof. Tsvi Kuflik[4], Prof. Einat Kodesh[7], Prof. Stefano Volpato[8], Prof. Tali Cukierman-Yaffe[1,2,9]

[1]Division of Endocrinology, Sheba Medical Center, Israel
[2]Epidemiology Department, School of Public Health, Faculty of Health, Tel Aviv University, Israel
[3]Department of Industrial Engineering, Tel Aviv University, Israel
[4]Department of Information Systems, University of Haifa, Israel
[5]Physical Therapy Clinic, Clalit Health Services, Israel
[6]Faculty of Health Sciences, Ariel University, Israel
[7]Department of Physical Therapy, University of Haifa, Israel
[8]Department of Medical Sciences, University of Ferrara, Italy
[9]Herczeg institute, Tel Aviv University, Israel

12:34-12:41 **Impaired Glucose Homeostasis in the Short-Telomere Telomouse**

Kamil Bar-Nes[1,2,3], Dr. Riham Smoom[2], Mr. Avinoam Gluck[2], Ms. Shiri Liluf[1], Mr. Mark Tigue[4], Prof. Benjamin Glaser[3], Prof. Klaus H. Kaestner[4], Dr. Dana Avrahami[1,3], Prof. Yehuda Tzfati[2,3]

[1]Department of Developmental Biology and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

[2]Department of Genetics, The Silberman Institute for Life Sciences, The Hebrew University of Jerusalem, Israel
[3]Department of Endocrinology and Metabolism, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel
[4]Department of Genetics and Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

11:45- 12:45	**Parallel Sessions - Posters** **Abstracts: Neuroendocrinology**	Hall D

Chairs: **Prof. Amit Akirov**, Associate Professor, Faculty of Medicine, Tel Aviv University, Israel
Endocrine Institute, Rabin Medical Center
Prof. Gil Levkowitz, Departments of Molecular Cell Biology, and Molecular Neuroscience, The Weizmann Institute of Science

11:45-11:52 **D2 Agonists as First Line Therapy for Nonfunctioning Pituitary Macroadenoma - A Single Center Experience**

Dr. Noa Sadigurschi[1], Dr. Elad Avraham[2], Dr. Uri Yoel[3,4], Dr. Vitaly Medvedovsky[3,4], Dr. Tamar Eshkoli[3,4], Dr. Lior Baraf[3,4], Dr. Rosa Novoa[4,5], Dr. Yuval Sufaro[2,4], Merav Fraenkel[3,4]

[1]Internal Medicine F, Soroka University Medical Center, Beer-Sheva, Israel
[2]Neurosurgery, Soroka University Medical Center, Beer-Sheva, Israel
[3]Endocrinology, Soroka University Medical Center, Beer-Sheva, Israel
[4]Faculty of Health Science, Ben-Gurion University of the Negev, Beer-Sheva, Israel
5Radiology, Soroka University Medical Center, Beer-Sheva, Israel

11:52-11:59 **A Combination of Computational and Experimental Tools Reveals Novel Mechanisms Regulating MKRN3, and its Function in GnRH-Secreting Mouse Neurons**

Dor Shalev[1], Dr. Lilach Pnueli[1], Ms. Gil Golan[1], Dr. Anat Kahan[2], Prof. Yael Mandel-Gutfreund[1,3], Prof. Philippa Melamed[1]

[1]Biology, Technion - Israel institute of technology, Israel
[2]Department of Animal Sciences, The Faculty of Agriculture, Food and Environment, The Hebrew University, Israel
[3]Faculty of Computer Science, Technion - Israel institute of technology, Israel

11:59-12:06 **The Challenge of Pre-Operative Radiological Diagnosis of Appendiceal Neuroendocrine Neoplasms: Implications for Conservative Management of Acute Appendicitis**

Dr.Orit Twito[1,2], Dr. Shai Ken-Dror[2,3], Dr. Maya Paran[2,4], Dr. Feda Fanadka[2,5], Dr. Rachel Chava Rosenblum[2,6], Dr. Adi Rov[2,7], Prof. Haim Pararn[2,7]
[1]Endocrinology, Wolfson Medical Center, Israel
[2]Sackler Faculty of medicine, Tel-Aviv University
[3]Surgery A, Meir Medical Center, Israel
[4]Department of pediatric and adolescent surgery, Schneider children's medical center
[5]Radiology, Meir Medical Center
[6]Endocrinology, Wolfson Medical Center
[7]Surgery A, Meir Medical Center

12:06-12:13 **Adrenal Insufficiency is Not a Common Cause of Hypoglycemia in Children**

Merav Gil Margolis[1], Mrs. Pearl Lilos[1], Prof. Moshe Phillip[1,2], **Prof. Liat de Vries**[1,2]

[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]Faculty of Medicine, Tel Aviv University, Israel

12:13-12:20 **Adopted Transgender Subjects Are Overrepresented and Have a Different Psychosocial Profile Than Their Non-Adopted Counterparts: A Case-Control Study**

Dr. Iris Yaish[1], Prof. Yona Greenman[1,2], Karen Tordjman[1,2]

[1]Institute of Endocrinology Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Israel
[2]Faculty of Medicine, Tel Aviv University, Israel

12:20-12:27 **Incidence, Temporal Trends, and Socioeconomic Aspects of Male Hypogonadism**

Dr. Ruth Percik[1], Dr. Shiraz Vered[2], **Prof. Yair Liel**[3]

[1]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Israel
[2]School of Public Health, University of Haifa, Haifa, Israel., Israel
[3]Faculty of Medicine, Ben-Gurion University of the Negev, Beer-Sheva, Israel

12:27-12:34 **Frequency of MC4R Pathway Variants in an Israeli Cohort of Individuals with Early-Onset Severe Obesity**

Michal Ben Ami[1], Dr. Tal Keidar[1], Dr. Eve Stern[1], Prof. Zohar Landau[2], Msc. Elinor Mauda[1], Msc. Noah Levek[1], Bsc. Noy Eli[1], Msc. Neria Levran[1], Dr. Noah Gruber[1,3], Prof. Orit Pinhas-Hamiel[1,3]

[1]Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medica Center
[2]Faculty of Health Sciences, Ben-Gurion University of the Negev
[3]School of Medicine, Tel Aviv University

12:34-12:41 **Overweight and Obesity in Survivors of Childhood Cancer**

Ms. Miriam Helin[1], Ms. Inna Zaslavsky-Paltiel[2], Dr. Michal Ben-Ami[3,4], Dalit Modan[3,4], Dr. Eve Stern[3,4], Prof. Liat Lerner[5]

[1]Faulty of Medicine, School of Public Health, Tel Aviv University
[2]Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center
[3]Pediatric Endocrinology, The Edmond and Lily Safra Children's Hospital
[4]Faculty of Medicine, Tel Aviv University
[5]Faculty of Medicine, School of Public Health, Tel Aviv University

11:45-12:45 Parallel Sessions - Posters Abstracts: Parathyroid and Bone Vitamin D — Hall E

Chairs: **Dr. Pnina Rotman**, Head, Institute of Endocrinology, Diabetes and Metabolic bone diseases Meir Medical Center
Dr. Nariman Saba Khazen, Head of the Endocrin Department Lin Medical Center Clalit Medical Services

11:45-11:52 **Endocrine Gland Size is Proportional to its Target Tissue Size**

Moriya Raz[1], Mr. Tomer Milo[1], Dr. David S. Glass[1], Dr. Avi Mayo[1], Prof. Uri Alon[1]

[1]Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

11:52-11:59 **Exploring a Rare Association: Pathophysiology and Treatment of Hypercalcemia in Non-Tuberculosis Mycobacterium Infections**

Dr. Viviana Ostrovsky[1], Dr. Ramon Cohen[2,3], Dr. Daniel Elbirt[3], Dr. Lior Zornitzki[4], Dr. Taiba Zornitzki[1]

[1]Hebrew University Medical School, Diabetes, Endocrinology and Metabolic Disease Institute, Kaplan Medical Center, Rehovot, Israel
[2]Hebrew University Medical School, Internal Medicine Department B, Kaplan Medical Center, & Department of Clinical Immunology Allergy and AIDS, Kaplan Medical Center, Rehovot, Israel
[3]Hebrew University Medical School, Department of Clinical Immunology Allergy and AIDS, Kaplan Medical Center, Rehovot, Israel
[4]Tel-Aviv University Medical School, Division of Cardiology, Tel-Aviv Sourasky Medical Center, Israel

11:59-12:06 **Osteitis Fibrosa Cystica Recovery Following Parathyroidectomy for Primary Hyperparathyroidism: A Case Series and Review of Literature**

Yehudit Eden-Friedman[1], Dr. Amna Jabarin[1], Dr. Gadi Shlomai[1], Dr. Iris Vered[1], Prof. Iris Eshed[2], Dr. Liana Tripro-Shkolnik[1]

[1]Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Israel
[2]Diagnostic Imaging, Sheba Medical Center, Israel

12:06-12:13 **Hyperglycemia Induces Cellular Senescence in Idg-Sw3 Osteocyte Like Cells**

Natan Lishinsky[1], Dr. Vladislav Temkin[1], Ms. Irina Gurt[1], Dr. Joshua Stokar[1], Prof. Rivka Dresner-Pollak[1]

[1]Department of Endocrinology and Metabolism, Hadassah - Hebrew University Medical Center, Israel

12:13-12:20 **Challenging Management of a Patient with Hypoparathyroidism**

Orly Agmon Gutin[1], Ms. Irene Unterman[2], Dr.Omer Hamtzany[1], Prof. Rivka Dresner Pollak[1]

[1]Endocrinology and Metabolism, Hadassah Medical Center, Israel
[2]Hadassah Medical Center, Israell

12:20-12:27 **Efficacy of a Computerized Therapeutic Decision-Making Algorithm in a Fracture Liaison Service Targeting Hip Fracture Patients**

Rachel Chava Rosenblum[1], Mr. Arthur Kogan[2], Dr. Dana Herzberg[1], Dr. Maysara Najjar[1], Dr. Oded Hershkovich[2], Dr. Orit Twito1, Dr. Raphael Lotan[2]

[1]Endocrinology Unit, Wolfson Medical Center, Israel
[2]Orthopedic Department, Wolfson Medical Center, Israel

12:27-12:34 **Vitamin D Down Regulates Cytokines Expression by the Immune System and its Possible Effect on Covid-19 Disease**

Prof. Shraga Shany[1]

[1]Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences., Ben Gurion University of the Negev, Beer Sheva, Israel

11:45- 12:45 Parallel Sessions - Posters Abstracts: Thyroid — Hall F

Chairs: **Dr. Avraham Ishay**, Haemek Medical Center Afula
Dr. Sagit Zolotov, Endocrine Institute, Rambam Health Care Campus, Haifa

11:45-11:52 **Methimazole for Prevention of Iodinated Contrast Media Induced Exacerbation of Thyrotoxicosis in Susceptible Patients**

Irit Ayalon-Dangur[1], Ms. Einat Magid-Ohayon[2], Dr. Noa Eliakim-Raz[3], Prof. Ilan Shimon[1], Prof. Eyal Robenshtok[1]

[1]Institute of Endocrinology, Rabin Medical Center, Israel
[2]Faculty of Medicine, Tel Aviv University, Israel
[3]Department of internal Medicine E, Rabin Medical Center, Israel

11:52-11:59 **Impact of Maternal Overt Hypothyroidism on Pregnancy Complications: A Nationwide Cross-Sectional Study**

Dr. Tamar Eshkoli[1,2], Mr. Nitzan Burrack[2,3], Mrs. Adi Gordon-Irshai[2,3], Mrs. Bracha Cohen[3], Dr. Uri Yoel[1,2], Dr. Merav Fraenkel[1,2]

[1]Endocrinology Unit, Soroka University Medical Center, Beer-Sheva, Israel
[2]Faculty of Health Science, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[3]Clinical Research Center, Soroka University Medical Center, Beer-Sheva, Israel

11:59-12:06 **Assessing the Clinical Impact of Molecular Testing in Bethesda V Thyroid Cases**

Idit Tessler[1], Dr. Tzahi Tzahi[1], Dr. Galit Avior[1]

[1]Department of Otolaryngology-Head and Neck Surgery, Sheba Medical Center

12:06-12:13 **Polyethylene Glycol Thyroid-stimulating Hormone (PEG-TSH) Testing in the Management of Pediatric Thyroid Dysfunction**

Dr. Hussein Zaitoon[1,2], Dr. Gabi Shefer[2,3], Dr. Anat Segev-Becker[1,2], Dr. Ori Eyal[1,2], Prof. Yael Lebenthal[1,2], Avivit Brener[1,2]

[1]Pediatric Endocrinology, Dana-Dwek Children's Hospital
[2]Faculty of Medicine, Tel Aviv University
[3]The Endocrine Laboratory, Tel Aviv Sourasky Medical Center

12:13-12:20 **Neoadjuvant Selective RET Inhibitor for Medullary Thyroid Cancer: A Case Report**

Miriam Steinschneider[1,2], Dr. Efrat Markus[1], Dr. Rutie Mamlok Sherf[1], Dr. Regev Landau[1], Dr. Limor Muallem Kalmovich[2,3], Dr. Raya Leibowitz[2,4], Dr. Shlomit Koren[1,2]

[1]Endocrine and Diabetes Institute, Shamir Medical Center, Zerifin, Israel
[2]Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[3]Department of Otolaryngology-Head and Neck Surgery, Shamir Medical Center, Zerifin, Israel
[4]Oncology Institute, Shamir Medical Center, Zerifin, Israel

12:20-12:27 **Subclinical Hypothyroidism in Elderly Patients Hospitalized in Acute Medical and Surgical Wards**

Dr. Vered Hermush[1,2], Dr. Shahar Bar[2], Dr. Jonathan Lellouche[1,3], Dr. Mark Niven[1,4]

[1]Adelson School Of Medicine, Ariel University
[2]Department of Geriatrics, Laniado Hospital
[3]Medical Laboratories, Laniado Hospital
[4]Endocrine Unit, Laniado Hospital

12:27-12:34 **Completion Thyroidectomy Practice: Can it be Avoided?**

Idit Tessler[1,2], Dr. Tzahi Yamin[2], Dr. Josh Krasner[3], Dr. Alon Eran[1,2], Dr. Galit Avior[4]

[1]Department of Otolaryngology-Head and Neck Surgery, Sheba Medical Center, Israel
[2]Tel-Aviv University, Tel-Aviv, Israel, Israel
[3]Department of Otolaryngology-Head and Neck Surgery, Jewish General Hospital, McGill University, Montreal, QC, Canda
[4]Technion University, Haifa, Israel

12:34-12:41 **The Association Between Elevated TSH Levels and Prolonged Length of Stay Among Adult Diabetic Patients Hospitalized in Internal Medicine Departments: A Large Historical Cohort Study**

MD candidate Aviel Kuchar[1], Dr. Tomer Ziv-Baran[2], Dr. Eugene Feigin[1,3], Dr. Elad Shemesh[3], Dr. Assaf Buch[1,3], Dr. Roy Eldor[1,3], Dr. Yona Greenman[1,3], Dr. Elena Izkhakov[1,3]

[1]Faculty of Medicine, Tel Aviv University, Israel
[2]Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Israel
[3]Institute of Endocrinology, Diabetes, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel

12:45- 13:45 **Lunch and & Visit the Exhibition**

13:45-16:00 **Plenary Session** Hall A

Chairs: **Prof. Gil Leibowitz**, President of the Israel Endocrine Society (IES),The Hadassah Diabetes Unit, Director. Department of Endocrinology
Dr. Merav Fraenkel, Head of Endocrine Unit, Soroka University Medical Center and Secertary of the Israel Endocrine Society

13:45-14:30 **New Insights in The Neuroendocrine and Central Response to Stress**
Prof. Alon Chen, Department of Brain Science, Department of Molecular Neuroscience, Weizmann Institute of Science

14:30-16:00 **IES Awards**

The Chowers Award | Dr. Avivit Brener

The Lindner Award | Prof. Yossi Tam

Best Mentors Award | Prof. Naomi Weintrob, Dr. Hannah Kanety

Best Community Physician Award | Dr. Hadassah Guttman

The Uri Liberman Award | Prof. Rivka Dresner-Pollak

Best Abstracts

16:00-16:20 **Refreshments & Visit at the Exhibition**

16:20-17:40 **Parallel Sessions**
Thyroid Tumors: Where are we in 2024?

Sponsored by: UNICTS

Hall A

Chairs: **Prof. Eyal Rubenshtock**, Endocrinology, Rabin Medical Center
Dr. Rena Pollack, Department of Endocrinology and Metabolism, Hadassah Medical Center

16:20-16:40 **Active Surveillance for Micro-PTC: Patient Selection and Follow-up**
Prof. Eyal Robenshtok, Endocrinology, Beilinson Hospital, Rabin Medical Center

16:40-17:00 **The Role of Radio Frequency Ablation in the Treatment of Thyroid Nodules**
Dr. Uri Yoel, Endocrinology, Soroka University Medical Center

17:00-17:25 **Thyroid Nodule Molecular Diagnostics: Current State and Future Applications**
(Recorded Lecture with Live Q&A)
Dr. Joshua Klopper, Medical Director, Endocrinology Veracyte, Inc.

17:25-17:40 **Specialist Panel- Discussion**

16:20-17:40 **Parallel Sessions**
Disease of the Adrenal Cortex, Medulla & HPA Axis

Hall B

Chairs: **Dr. Orit Twito**, Head, Endocrinology and Diabetes, Wolfson Medical Center
Dr. Leonard Saiegh, Bnai Zion Medical Center; Technion Faculty of Medicine

16:20-16:50 **Local and General Experience With ACC-A Clinical Update**
Dr. Ofra Mimon, Head of Oncology Day Care Unit, Hadassah Medical Center

16:50-17:10 **Ectopic Cushing's Syndrome - What's New?**
Dr. Etty Osher, Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center; Head of Neuroendocrine Tumor Service

Sponsored by: MEDISON

17:10-17:40 **Familial Pheochromocytoma/Paraganglioma syndromes - From the Bench to the Clinic and Beyond**
Prof. Amit Tirosh, Head, Neuroendocrine Oncology Unit Director, ENTIRE - Endocrine Neoplasia Translational Research Center; Sheba Medical Center and Tel Aviv University Faculty of Medicine

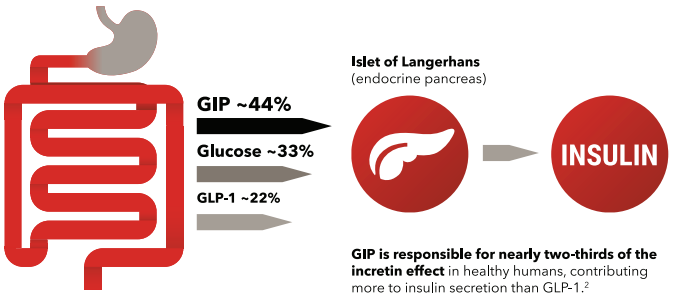
POWER OF GIP

Lilly

גלו את עוצמתו של GIP
בבקרה על גלוקוז ומשקל הגוף

GIP אחראי על כשני שליש מהאפקט האינקרטיני באוכלוסיה הבריאה,
עם השפעה גדולה יותר על הפרשת האינסולין בהשוואה ל-GLP-1.[1]

~2/3



GIP is responsible for nearly two-thirds of the incretin effect in healthy humans, contributing more to insulin secretion than GLP-1.[2]

Reference: 1. Nauck MA, Meier JJ. Diabetes. 2019;68(5):897-900. **2.** Nauck MA, Meier JJ. Diabetes. 2019;68:897-900

PP-LD-IL-0152

אימסיברי (סטמלנוטייד)

התכשיר הממוקד הראשון לטיפול ברעב בלתי נשלט והשמנת יתר חולנית מגיל צעיר הנגרמת כתוצאה מפגם במסלול הרעב ושובע MC4R, בחולי תסמונת ברדט-בידל ומצבים גנטים נוספים[1].

- ירידה משמעותית וממושכת ברעב[2]
- ממוצע ירידה של 0.8 במדד BMI Z-score בילדים מגיל 6 ומעלה, במשך 52 שבועות[2]
- ממוצע ירידה של 9.1% במדד BMI במבוגרים מגיל 18 ומעלה, במשך 52 שבועות[2]
- שיפור קליני משמעותי במדדי איכות חיים:
  תפקוד פיסי, הערכה עצמית, מצוקה חברתית, תפקוד מיני ותפקוד בעבודה[3]

> **אימסיברי הוכרזה כתרופת יתום ו-טיפול פורץ דרך במחלות השמנה על רקע פגם במסלול MC4R**
> FDA - News Events Human Drugs 2022

> **אימסיברי הוכללה בקטגוריית תרופות עם תרומה יוצאת דופן לבריאות הציבור**
> EMA - Human Medicines Highlights 2021

הפניות:
1. עלון לרופא כפי שאושר ע"י משרד הבריאות, אוגוסט 2023.
2. Haqq AM, et al. Lan Diabetes Endocrinol. 2022;10(12):859-866.
3. Forsythe E, et al. Orphanet J Rare Dis. 2023;16(1):12.

למידע נוסף יש לפנות לעלון לרופא כפי שאושר על-ידי משרד הבריאות

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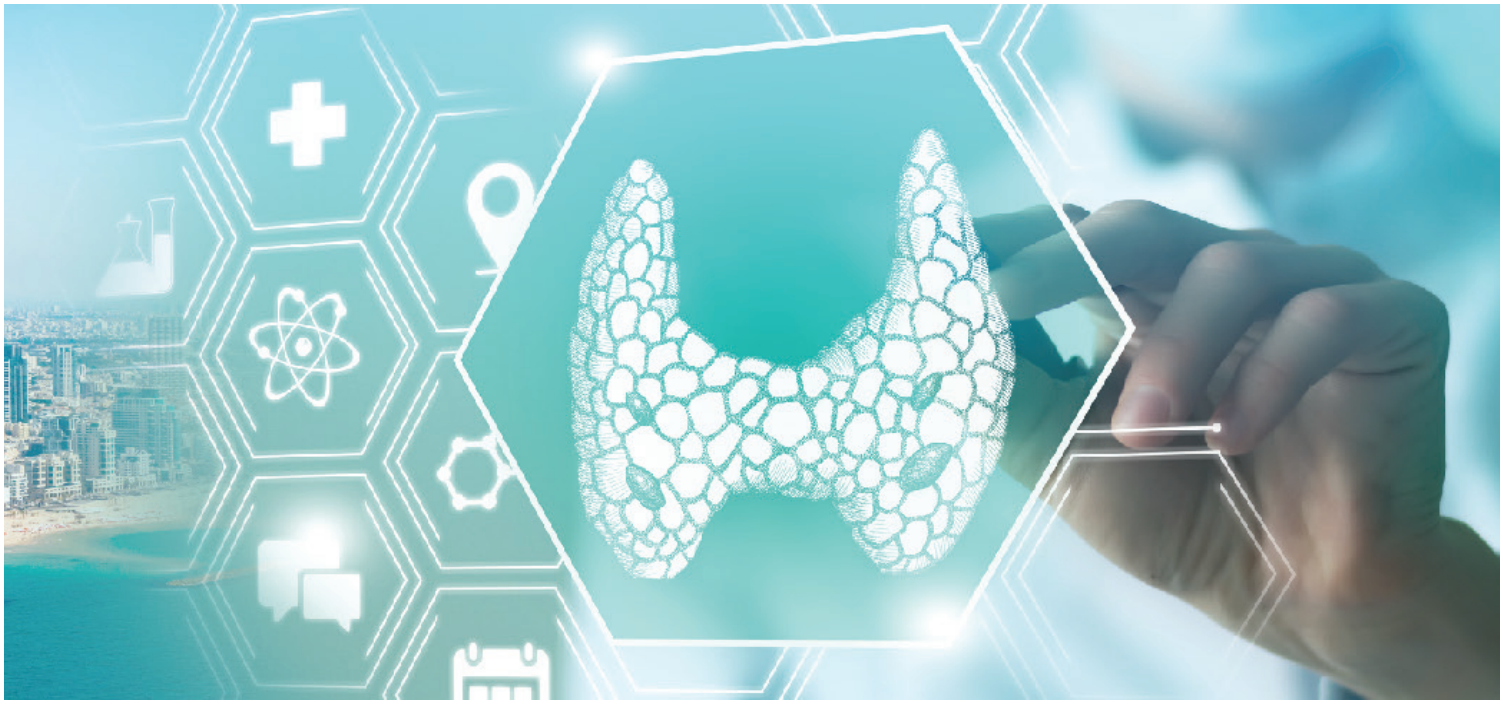

ABSTRACTS

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Endogenous Cushing's Syndrome and Cancer Risk: a Nationwide Israeli Cohort Study

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Background:

There are no clear data on the association between Cushing's syndrome (CS) and cancer risk. We aimed to assess the risk of cancer in CS patients, compared with matched controls.

Methods:

We conducted a nationwide retrospective cohort study of patients with endogenous CS diagnosed during 2000–2023, using the electronic health record database of Clalit Health Services, Israel.
All patients had an ICD-10 diagnosis of CS and biochemical evidence of hypercortisolism and were classified according to disease source as pituitary CS, cortisol-secreting adrenal adenoma, or indeterminate source. Patients with adrenal cancer or ectopic CS were excluded.
Patients with CS were individually matched in a 1:5 ratio according to age, sex, socioeconomic status, and body-mass index.
The primary outcome was first diagnosis of any malignancy following CS diagnosis, calculated using the Fine and Gray hazards model with death as a competing event.

Results:

The study cohort included 609 CS patients and 3018 matched controls [mean age at diagnosis, 48.0±17.2; 2371 (65.4%) women; median follow-up, 14·7 years (IQR 9·9–20·2)]. Of these, 251 (41.2%) patients had pituitary CS, 200 (32.8%) patients had adrenal CS, and in 158 (25.9%) cases the source was indetermined.
At baseline, 50 (8.2%) CS patients and 117 (3.9%) controls had a history of prior malignancy (p0.05), mainly due to malignancies diagnosed within 5 years of CS diagnosis (5.9% vs. 2.2%, p0.05), while there was no difference in the rate of malignancies diagnosed more than 5 years prior to CS diagnosis (2.3% vs. 1.7%, p=0.32).
During follow-up [median, 14.7 years (IQR 9.9–20.2)], the risk for cancer was higher for CS patients compared with their matched controls (hazard ratio [HR], 1.78, 95% CI 1.44-2.20, p0.01).
The risk for malignancy was elevated in patients with pituitary CS (HR 1.65, 95% CI 1.15-2.36, p0.01) and in patients with adrenal CS (HR 2.36, 95% CI 1.70-3.29, p0.01).
The risk for malignancy was higher among patients with pituitary CS who did not achieve early remission (n=69) compared with those in remission (n=99) [unadjusted HR 3.89 (95% CI 1.41-10.75, p=0.01)]. The unadjusted HR in patients with adrenal CS who did not achieve early remission (n=39) compared with those in remission (n=113) was 1.68 (95% CI 0.83-3.40, p=0.17).

Conclusion:

Endogenous Cushing's syndrome is associated with increased cancer risk.
Our data suggest that early biochemical remission, particularly in patients with pituitary CS, may attenuate this risk.

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Predicting childhood obesity from maternal thyroid-related parameters via machine learning

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Background:

Childhood obesity (CO) and iodine deficiency (ID) are prevalent in developed countries, including Israel. It has been demonstrated that CO is associated with adverse health outcomes in adulthood. Also, it was recently suggested that mild-to-moderate ID and insufficient maternal iodine status may increase the risk of large-for-gestational (LGA) newborns. In spite of the fact that LGA has been established to have an influence on CO during pregnancy, it remains difficult to predict CO during pregnancy.

Aim:

To directly predict CO from anthropometrics, thyroid function tests, iodine status, and iodine intake related parameters of pregnant mothers with mild-to-moderate ID.

Methods:

A prospective study of 192 mother-child pairs was conducted. Maternal iodine status and thyroid function were detected during the second half of pregnancy, including serum thyroglobulin (Tg). Using a semi-quantitative iodine food frequency questionnaire, maternal iodine intake was assessed. The anthropometric measurements were obtained from pregnant women in late pregnancy and from their offspring at two years of age (a gender-adjusted weight percentile of 85% was considered overweight). We created five different synthetic datasets using the Synthetic Minority Oversampling Technique (SMOT) to compare the performance of six different machine learning (ML) algorithms (Artificial Neural Networks, Random Forests, Decision Trees, Penalized Logistic Regression and Support Vector Machines).

Results:

Selected anthropometric (height), thyroid-related (Tg), demographic (education level, religiosity and age) and nutritional (yellow cheese consumption and estimated iodine intake from yogurt) maternal data successfully predicted offspring overweight at two-years.

Conclusion:

In pregnant mothers with mild-to-moderate ID, ML may be able to predict offspring overweight at two years of age (an indicator of CO). These findings, if further investigated and validated, could lead to treatments that reduce CO incidence in Israel and elswhere.

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Mody and type 1 Diabetes mellitus – can the two walk hand in hand?

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Y is 35 years old man, diagnosed with type 1 DM at the age of 16 after hospitalization due to DKA and positive GAD antibodies.

His diabetes was never well controlled and there is a strong family history of diabetes and prediabetes as described below:

His father and brother are prediabetic. The father diagnosed at age 50 and the brother is prediabetic since the age of 17 (~ 30 years).

Three of His brother Childrens, ages 8-18 have A1c of 6.5.

Two parental cousins are prediabetic and one cousin has type 1 DM with positive antibodies.

Recently, Y`s daughter aged 3, was diagnosed with an A1c of 6.6%, asymptomatic.

All the above-mentioned persons were found to have negative GAD antibodies and are kept on a diet only with no diabetic complications, with impaired fasting glucose permanently (except the cousin with type 1 of course)

After his little daughter was diagnosed with diabetes Y asked to check himself for Monogenic Diabetes so we did exome panel for monogenic diabetes at Maccabi health services.

The test (NGS) was performed at Sheba center.

Surprisingly or not, the genetic testing was inconclusive positive for heterozygote GCK gene. highly pathogenic Mody for type 2.

All family members were referred to complete exome panel, which is not yet complete.

In literature I found one case report from the UK in 2014 (attached) about a 14-year-old Caucasian boy who diagnosed with both T1DM and later on MODY type 2, same as our patient.

The author’s conclusion from this case was that one should use higher glucose thresholds levels for these patients because use of high Insulin dose may render them with symptomatic hypoglycemia at blood glucose levels considered to be normal.

My **conclusion** from this fascinating case: as we are diagnosing more and more monogenic diabetes cases, we should be aware that both diabetes types can exist side by side and the insulin treatment must be adapted according to a higher glucose levels as mentioned before.

In addition, we must have a high level of suspicion for these complex cases which are still not common at all.

Outcomes in Maternal Graves' Disease: A Population-Based Mother-Infant Dyad Cohort Study

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Background:

Graves' disease has been associated with adverse pregnancy, labor and delivery, and neonatal outcomes. Thyroid function levels, assessed during newborn screening (NBS), can serve as indicators of the adaptation in the hypothalamic–pituitary–thyroid axis. We utilized data from the national thyroid NBS program to investigate the characteristics of the mother-infant dyad of term infants born to mothers with past or active Graves' disease.

Methods:

The dataset of the Israeli NBS for thyroid function was linked with the electronic records of a tertiary medical center to generate a unified database of mothers and their term infants born between 2011 and 2021. The MDClone big data platform extracted maternal, pregnancy, disease course, labor and delivery, and neonatal characteristics of the mother-infant dyads.

Results:

Out of 103,899 registered mother–infant dyads, 292 (0.3%) mothers had past or active Graves' disease. A forward multivariate linear regression demonstrated that Graves' disease did not significantly affect NBS total thyroxine (tT4) levels ($p = 0.252$). NBS tT4 levels in infants born to mothers with active Graves' disease were higher than those observed in the general Israeli population ($p < 0.001$). Mothers with Graves' disease more frequently used assisted reproductive technology (12.7% vs. 9.0%, respectively, $p = 0.012$; odds ratio [OR] = 1.46 [CI 1.03–2.07], $p = 0.031$), and had more gestational hypertension (3.9% vs. 1.1%, $p < 0.001$; OR = 3.53 [CI 1.92–6.47], $p < 0.001$), proteinuria (2.5% vs. 0.9%, $p < 0.001$; OR = 3.03 [CI 1.43–6.45], $p = 0.004$), cesarean sections (26.4% vs. 19.7%, $p = 0.029$; OR = 1.46 [CI 1.13–1.90], $p = 0.004$), prelabor rupture of membranes (15.4% vs. 4.1%, $p < 0.001$; OR = 4.3 [CI 3.13–5.91], $p < 0.001$), and placental abnormalities (5.1% vs. 2.0%, $p < 0.001$; OR = 2.64 [CI 1.57–4.44]; $p < 0.001$). Their infants had lower adjusted birthweight z-scores (-0.18 – 0.94 vs. -0.03 – 0.90, $p = 0.007$) and were more likely to be small for gestational age (12.0% vs. 8.1%, 5; OR = 1.54 [CI 1.08–2.19], $p = 0.018$).

Conclusions:

Neonatal thyroid function levels were affected by maternal Graves' disease only when the disease was active during gestation. Moreover, maternal Graves` disease was also associated with an increased risk of adverse outcomes for the mother-infant dyad.

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Low Dose Sublingual Estradiol Decreases Protein S, Generating a Potentially Pro-Thrombotic State: Interim Results of a Controlled Prospective Pilot Study of Treatment-Naïve Trans Women.

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Background:

Sublingual (SL) estradiol (E) for gender-affirming hormone therapy (GAHT) of transgender women (TW) might obviate the need for an anti-androgen, and mitigate pro-coagulant changes. We recently showed that SL 2 mg E, divided into 4 daily doses (SLE), offers no clinical advantage over the same dose given orally in combination with cyproterone acetate (CPA). Furthermore, we showed that after each SL administration, serum E2 (sE2) peaked to levels, the likes of which are achieved only during induction of ovulation with gonadotrophins.

Hypothesis and Aim:

Given the exceedingly high peak sE2 measured under SL-GAHT, we hypothesized it could lead to partial acquired Protein S deficiency, a recognized pro-thrombotic state and risk factor for venous thromboembolic events (VTE). Our aim was to assess the hemostatic system under SLE in comparison with the standard combined oral (CO) approach.

Design and Methods: In this ongoing open label study, treatment-naïve TW are assigned in a 1:1 ratio (15 in each arm) to either standard CO (2 mg E2 with 10 mg CPA once daily), or to 2 mg sublingual E divided into 4 daily dose for 6 months (6M). An extensive battery of hemostatic biomarkers, including free Protein S antigen (fPS), are assessed at baseline (BL) and at 6M.

Results:

We herein report on 27 subjects (15 CO/12 SLE) who initiated treatment, 17 of whom have already completed it.

The median age of the cohort is 20 y (IQR 19-27; range 18-42]. There were no BL differences between the groups.

At 6M, none of the hemostatic markers differed between the groups except for fPS, which was significantly lower in the SL group 79.7±11.6% vs. 104.6±5.6%, P=0.039. By paired comparisons for the entire group, fPS decreased from 104.2±5.2% at BL to 95.8±5.9% at 6M, P=0.003. This was entirely accounted for by the change in the SLE group, in which fPS went down from 95.7±10.3% to 79.7±11.6%, P0.001; with some values reaching the fPS deficiency range. In contrast, fPS, remained unchanged under CO 108.9±5.7% and 104.5±5.2%, at BL and 6M respectively, P=0.153.

Conclusions:

The most notable interim finding was a clinically significant decrease in fPS under low dose SLE. Given the extreme peaks of sE2 we previously reported with this protocol, an acquired deficiency of this natural anti-coagulant was expected.

These preliminary findings support our hypothesis, and raise the concern that GAHT of TW with chronic SLE might carry an increased long-term risk for VTE.

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Adopted transgender subjects are overrepresented and have a different psychosocial profile than their non-adopted counterparts: a case-control study.

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Background and Aim:

We previously demonstrated (1) that in our transgender clinic, adoptees are significantly overrepresented compared to the general population, suggesting early life traumas may play a role in the etiology of transgenderism. We had also shown a large preponderance (close to 80%) of female sex-assigned-at-birth (SAB), and a trend for presenting for treatment at an older age than non-adopted subjects. In the current study we aimed to further characterize this subgroup by comparing them to contemporary, non-adopted matched control subjects.

Subjects and Methods:

Between 01.05.2014 and 31.12.2022, 671 new adult subjects presented to our center for gender-affirming hormonal treatment (GAHT), 14 of whom were adoptees (2.09%). These were matched in a 1:4 for age and SAB, with non-adopted transgender subjects from the same cohort. The 2 groups were compared for multiple psychosocial and life-style characteristics. Comparisons of categorical variables were performed by cross-tabulation statistics.

Results:

By design, the current age of subjects (25.0±6.1 y] range 20-40), and the age at initiation of GHAT (22 y [IQR 20-27.5]), were identical, but so was the mean age of dysphoria onset (10 y, range 3-30); 77.1% were transgender men.

Groups did not differ with respect to their marital status, altogether 75.7% were single, none had biological children. Adoptees came from families with significantly higher socioeconomic status (SES), 28.6% from high SES vs none among controls. Despite this, none of the adoptees had any college education vs. 28.3% of the controls (P=0.028). Employment rate, however, was generally similar in both groups at 72.1% of the cohort.

Adoptees tended to carry a psychiatric co-morbidity more often (57.1% vs 28.6%, P=0.061). The number of psychiatric co-morbidities was also higher among adoptees (0.38 per subject vz 0.79, P=0.042). Among non-adopted subjects only 62.2% were still living with their parents, as opposed to only 21.4% of adoptees (P=0.013).

Lastly, adoptees were more often smokers (57.1% vs. 16.4%, P=0.004), and cannabis users (21.4% vs. 1.9%, P=0.028).

Conclusions:

Adoptees are not only overrepresented among the transgender population treated at our center, but they also have a more fragile psychosocial profile despite coming from higher SES families. These observations might shed some light into the etiology of transition among adoptees that should prompt further exploration. Additionally, they should heighten the attention of clinicians to the vulnerability of this special population.

1. Yaish I, Keltch G, Greenman Y, Kolitz T, Tordjman K. doi: 10.1210/jendso/bvad114.2065

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Low Dose Estradiol Gender-Affirming Hormone Therapy (GAHT) Generates Rapid Feminizing Body Changes in Transgender Women: A Dual Energy X-Ray Absorptiometry-Based Prospective Study

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Background and Aim:

We previously demonstrated that low-dose estradiol (E2) administered sublingually alone for 6 months in treatment-naïve trans women (TW), suppressed testosterone to the same degree, but generated higher serum E2 levels as the same oral dose combined with cyproterone acetate. We now sought to assess the possible differential impact of these approaches on anthropometric and body composition measurements, sex-dependent indicators with proven metabolic prognostic value.

Methods:

22 treatment-naïve TW, 23.2± 1.1 y, opted non-randomly, in a 1:1, ratio to receive sublingual E2 (2mg divided into 4 daily doses), or oral 2 mg E2+10 mg cyproterone acetate for 6 months (6M). Anthropometric, hormonal, and body composition by DXA (Lunar Prodigy-GE) measurements were obtained at baseline, and after 6M of GAHT.

Results:

Anthropometric, body composition measurements, and testosterone at baseline and 6M did not differ between the groups. In a first step, all subjects were analyzed together for assessment of the general impact of GAHT.

By paired comparisons, neither weight nor BMI had changed at 6M. Hip circumference remained unchanged, however, waist circumference decreased by 2.7±1.19 cm (P=0.047), resulting in a significant reduction in waist-to-hip-ratio (P=0.018).

The total regional fat percentage increased from 23.4±2.3% to 27.8±1.8% (P0.001). This increase was significant for all fat depots (gynecoid, arms, legs, trunk) except for the android area. Total body fat mass increased by 2.6 kg, from 18.4±2.4 to 21.0±2.4 kg (P=0.008).

In contrast, subjects lost lean mass in all compartments. The whole body lean mass loss was 3.4±0.3 kg (a 21.6% decrease, P0.001), leading to a decrease in the lean/fat mass ratio from 4.7 to 2.9, (P=0.0002).

Analyzed separately, some changes appeared to be influenced by the treatment route, particularly the increases in fat depots that were significantly milder in the sublingual group. The lean body mass decrease, however, was similar with both treatments.

After age-adjustment, none of the variables at 6M correlated with hormone levels. However, decreases in total body, legs, and arms lean mass were inversely correlated with testosterone at 6M (r=-0.41, P=0.045; r=-0.476, P=0.033; and r=-0.563, P=0.01, respectively).

Conclusions:

A relatively short GAHT period with a low dose of E2 generated significant body feminization in TW.

Subjects in the sublingual group were surprisingly spared from body fat accumulation. The reason for this differential effect of sublingual E2 is still unknown.

Sublingual E2 could offer some protection from fat accumulation but not from lean body mass loss in TW.

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Efficacy of a computerized therapeutic decision-making algorithm in a Fracture Liaison Service targeting hip fracture patients

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Background:

Osteoporotic fracture risk is doubled in patients with recent fracture; however, post-fracture treatment rates remain dismal. Fracture Liaison Services (FLS) aim to close the secondary prevention 'gap' and reduce risk of further fractures. Multiple FLS models exist throughout Israel, however many institutions remain without active programs. This study evaluates the feasibility and efficacy of a computer algorithm-supported, Nurse Practitioner-run FLS developed in Wolfson Medical Center (WMC).

Methods:

An FLS decision-making algorithm was developed by the WMC endocrinology team using zoledronic acid as the default medication, and recommending endocrinology consultation for patients younger than 65 years, with estimated glomerular filtration rate (eGFR) 35 and/or prior osteoporosis therapy. The protocol was computerized and integrated into the Chameleon Electronic Medical Record (EMR) system (Elad diagnostics, Israel) as a component via collaboration with the Directorate of Government Medical Centers of the Israeli Ministry of Health. The algorithm is run by a Nurse Practitioner, who orders endocrinology consultations when necessary. Patients with vitamin D deficiency/insufficiency are given a loading dose. This retrospective study assesses utility of the algorithm in hip fracture patients hospitalized in WMC between 01/04/2023-31/10/2023. Data extracted from computerized patient files includes age, gender, fracture type, laboratory test results, use and results of the computerized algorithm, endocrinology consultations, and administration of a vitamin D loading dose.

Results:

Two-hundred and eight hip fractures were identified during the study period. The cohort was predominantly female (137/208, 65.9%); mean age was 79.9 ± 9.6 years. Nurse practitioner evaluation was performed in 200/208 patients (96.2%). Of these, the algorithm provided a treatment recommendation in 140/200 (70.0%), while 60/200 (30.0%) required endocrinology consultation due to prior therapy)31/60, 51.7%), low eGFR (20/60, 33.3%), and/or age below 65 years (12/60,20.0%). Patients requiring endocrinology consultation were more likely to be female and had lower eGFR. Treatments recommended by consultation were zoledronic acid (21/60, 35%), denosumab (3/60, 5%), and teriparatide (1/60, 1.7%); further investigations were recommended in 23/60 (38.3%) and no therapy in 8/60 (13.3%). Vitamin D deficiency/insufficiency was present in 161/202 (79.7%), and loading dose given in 89/99 (89.9%) deficiency and 44/62 (71.0%) insufficiency cases.

Discussion:

This streamlined, computerized algorithm-based FLS model was practical and functional; the algorithm provided therapeutic recommendations in 70% of cases without need for physician intervention. This simple FLS intervention has the capacity for broad distribution throughout Israel, is easy to implement and its maintenance requires minimal healthcare worker load.

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Paragnglioma: a series of 8 cases in a single center

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Introduction:

Paraganglioma (PGL) is a rare neuroendocrine tumor that arise in the parasympathetic or sympathetic ganglia. According to the WHO classification 2017, all PGLs are considered to have metastatic potential. Up to 60% of patients carry a germline or somatic mutation that can influence treatment and follow-up. Therefore, all patients should be referred for a genetic evaluation. Although parasympathetic PGLs are usually "silent", all suspected PGLs should undergo biochemical workup. For these reasons and more, PGLs require multidisciplinary management and treatment by experienced endocrinologist, radiologist, surgeon, pathologist and genetic expert.

Aim:

To evaluate the multidisciplinary medical management of PGL`s in our institute.

Methods:

We conducted a computerized search in Shamir medical center database for the diagnosis of paraganglioma from 2008-2023. Out of 12 patients with suspected paraganglioma, we included 8 patients who had positive pathology for paraganglioma. Clinical, biochemical, radiologic and pathologic information was collected.

Results:

8 patients (50% female) aging 40-73 (mean 52) were pathologically diagnosed with PGL. 50% (4/8) with head and neck PGLs (carotid body tumors) and 50% (4/8) with abdominal extra-adrenal tumors. 12.5% (1/8) diagnosed with a metastatic disease and 12.5% (1/8) had a recurrence after 22 months. 37.5% (3/8) were asymptomatic. Symptoms were mainly related to local pressure (such as abdominal pain and neck enlargement). 25% (2/8) had an endocrine assessment (EA) prior to surgery and extra 25% (2/8) had EA post-surgery. 25% (1/4) was positive for urinary dopamine, 100% (4/4) were negative for urine metanephrines and normetanephrines. 50% (4/8) had functional imaging (2 before surgery). Only 25% (2/8) were referred for a genetic consultation. 85.7% (6/7) continued follow-up. Even though they all had a radiological follow-up (7-124 months, median 51.5), only 42.8% (3/7) continued biochemical and endocrinological follow-up (1 was referred to a tertiary NET unite). During Follow-up, mortality was 14.3% (1/7) for unknown reason.

Conclusions:

PGL is a rare disease, which requires higher awareness for multidisciplinary management and follow-up, and all the patients should be referred for genetic evaluation.

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Cortisol secretion in obesity revisited: lower basal serum free cortisol with diminished cortisol response to the low dose 1ug ACTH challenge

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Objective:

Some clinical resemblance may exist between obesity, particularly abdominal obesity, and Cushing's syndrome. This has stimulated ongoing interest in the role of cortisol`s secretion pattern, control and metabolism in obesity.

Goals:

To compare basal and dynamic cortisol response to an intravenous bolus dose of 1 ug ACTH in healthy obese versus lean controls

Design:

Total, free and salivary cortisol were tested at the basal state and after a standard challenge with 1 ug ACTH in 60 healthy obese subjects (mean BMI= 39 kg/m2) and 54 healthy lean controls (mean BMI=23 kg/m2).

Results:

Basal total cortisol was significantly lower in obese as compared to lean subjects [361.56+/-132 vs 414+/-121 nmol/L; p=0.019]. Additionally, baseline total cortisol and salivary cortisol were inversely related to BMI (r=-0.24, r=-0.27; p0.05 for both). Baseline total and salivery cortisol were also negatively correlated with waist circumference (r=-0.27, r= -0.34; p0.05 for both). Upon challenge with ACTH, total and salivary cortisol response were significantly lower in obese than in lean subjects [665.16+/-151.8 vs. 728.64+/- 124.2 nmol/L, p0.05; 31.66 (19-38.64) vs. 40.05 (31.46-46.64) nmol/L, p0.05].

Conclusion:

Basal as well as peak stimulated cortisol and integrated post-1ug ACTH-stimulated total serum cortisol levels were significantly lower in obese subjects. Obesity is not associated with enhanced basal cortisol or ACTH-stimulated cortisol reserve. Hence, increased serum or salivary cortisol is atypical for uncomplicated obesity.

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Impact of etiology, sex and remission status on erythrocytic profile in patients with Cushing's syndrome: a large population database study

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Objective:

As glucocorticoids are known to stimulate erythropoiesis, Cushing's syndrome (CS) has various effects on hematological parameters. Our study aimed to characterize the erythrocytic profile in patients with CS versus the normal population and describe dynamics according to etiology, sex and remission status.

Methods:

This retrospective cohort analysis, using data collected from Clalit Health Services, compared erythrocytic parameters between patients with CS of pituitary (Cushing`s disease, CD) and adrenal (aCS) etiology and age, sex, body mass index (BMI) and socioeconomic status-matched controls in a 1:5 ratio. Patients with ectopic CS and adrenal carcinoma were excluded. Laboratory values at baseline were calculated as mean values during the year preceding CS diagnosis, and over one year thereafter.

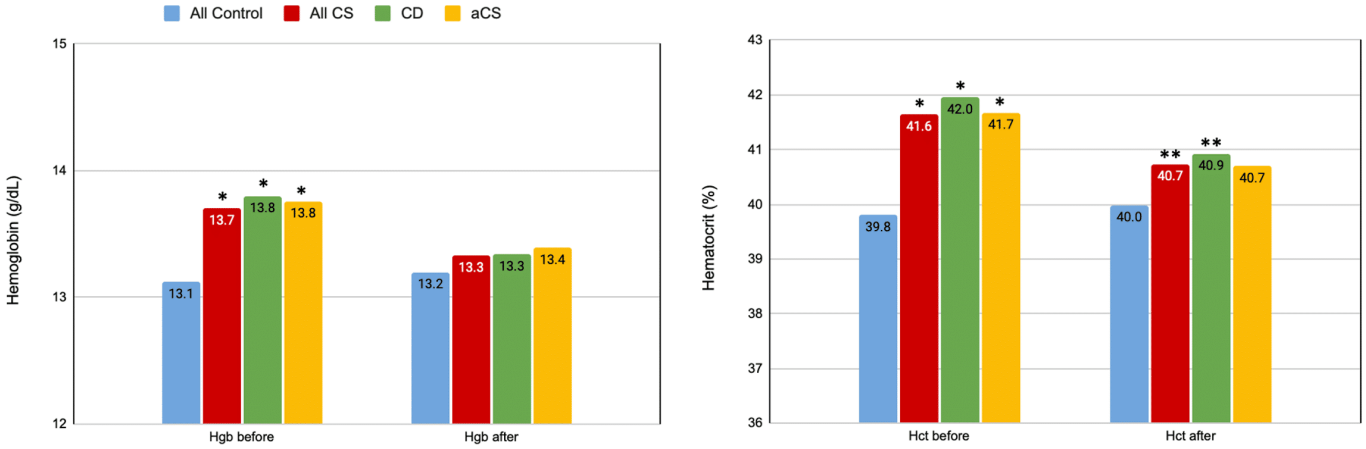
Results:

The cohort included 397 patients with CS and 1970 controls. The mean age at diagnosis for CS group was 51.11±16.85 years and BMI was 31.15±7.76 kg/m^2. The mean number of blood tests available at baseline and a year after diagnosis was 3.8±4.9 and 4.9±4.6 in CS patients, and 2.2±3.1 and 2.5±5.5 in controls. Patients with CS had significantly higher baseline median levels of hemoglobin (Hgb) and hematocrit (Hct) compared to controls (Hgb: 13.70 [12.70-14.65] g/dL vs. 13.12 [12.30-14.10] g/dL [*p*0.0001] and Hct: 41.64 [38.77-44.51]% vs. 39.80 [37.30-42.70]% [*p*0.0001]). These differences were observed for patients with both CD and aCS and for both sexes. Within a year following diagnosis, patients who attained remission had Hgb and Hct levels comparable to control counterparts; Hgb was 13.20 (12.33-14.30) g/dL in CD and 13.20 (12.17-14.00) in aCS, versus 13.20 (12.20-14.10) g/dL in controls. Similarly, Hct was 40.08 (37.30-42.75)% in CD and 40.08 (37.65-42.30)% in aCS upon remission, compared to 39.98 (37.30-42.60)% in controls. Meanwhile, those with persistent/recurrent disease maintained elevated levels relative to those who attained remission; patients with CD without remission had levels of 13.75 (13.03-14.72) g/dL (*p*=0.0567) and 42.45 (39.50-44.48)% (*p*=0.0049), and aCS patients had similar results that did not reach significance (Hgb: 14.08 [12.70-14.59] g/dL and Hct: 42.40 [37.80-44.88]%, [*p*=NS]).

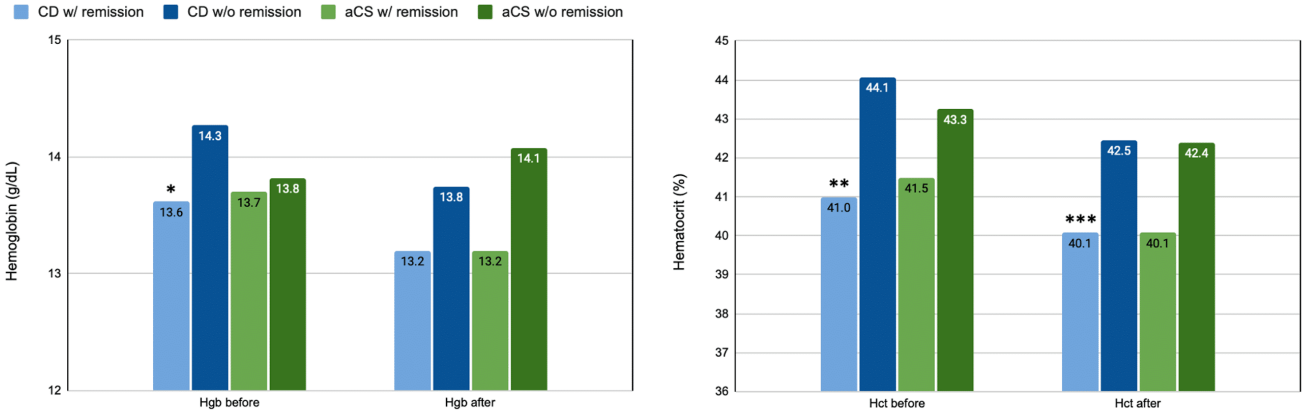
Conclusions:

In our study, the largest to date, selected erythrocytic parameters such as Hgb and Hct are significantly higher in patients with CS versus normal controls in both sexes and regardless of etiology. These parameters normalize post-remission in CD. Our data illustrates that erythrocytic parameters are influenced by endogenous glucocorticoid excess and potentially can be used as additional markers for remission.

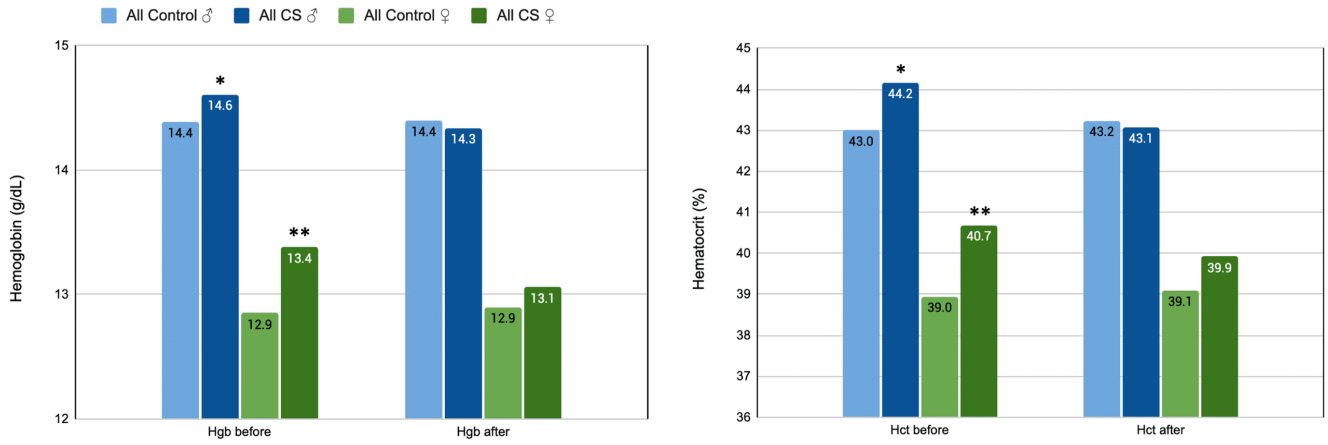
Median hemoglobin and hematocrit a year before and after diagnosis



Median hemoglobin and hematocrit change according to remission status



Median hemoglobin and hematocrit change according to sex



Characteristics of patients with CS and controls

	Controls	Patients with CS	p-value
N	1970	397	
BMI at diagnosis, kg/m^2 mean±SD	30.15±6.98	31.15±7.76	0.1414
BMI 1 year after diagnosis, kg/m^2 mean±SD	30.84±7.28	32.26±9.67	0.2115
Age, years mean±SD	51.06±16.86	51.11±16.85	0.969
Gender N (%)			0.906
Male	618 (31.37)	126 (31.74)	
Female	1352 (68.63)	271 (68.26)	
Socioeconomic status N (%)			0.996
Low	252 (13.66)	51 (13.71)	
Medium	1122 (60.81)	227 (61.02)	
High	471 (25.53)	94 (25.27)	
Smoking status N (%)			0.04
Never	791 (63.43)	171 (61.73)	
Past smoker	250 (20.05)	44 (15.88)	
Current smoker	206 (16.52)	62 (22.38)	
Comorbidities at diagnosis N (%)			
Diabetes mellitus	327 (16.60)	113 (28.46)	<0.001
Hypertension	772 (39.19)	263 (66.25)	<0.001
Dyslipidemia	722 (36.65)	215 (54.16)	<0.001
Ischemic heart disease	167 (8.48)	59 (14.86)	<0.001
Stroke	73 (3.71)	24 (6.05)	0.037
Cardiovascular disease	223 (11.32)	77 (19.4)	<0.001
Chronic kidney disease	73 (3.71)	25 (6.30)	0.026
Malignancy before diagnosis	103 (5.23)	45 (11.34)	<0.001
Malignancy after diagnosis	213 (10.81)	67 (16.88)	0.001

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Adrenal insufficiency is not a common cause of hypoglycemia in children

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Background:

Hypoglycemia etiology in children is heterogeneous and varies by age. Both growth hormone (GH) and cortisol deficiencies may present with hypoglycemia; the latter may result in an adrenal crisis that may be fatal.

Objectives:

To evaluate responses of cortisol and GH to spontaneous hypoglycemia in infants and children, and to assess the rate of true cortisol deficiency in children, defined as cortisol500 nmol/l.

Study design:

This retrospective study included 127 children (0-18 years old) who presented with hypoglycemia during 1992-2022, and who had a serum laboratory glucose level ≤50 mg%.

Results:

Cortisol 500 nmol/l was detected in critical samples of 50% (n=64) of the patients, and cortisol 270 nmol/L in 12.2% (n=29). A normal cortisol response to Synacthen stimulation was observed in 93.7% (n=119). Compared to the rest of the cohort, among children with cortisol levels 500 nmol/L, the median GH level in the critical samples was higher (6.0 vs. 3.4 ng/ml, p0.037), and insulin was detected more frequently (59.6% vs. 35.6%, p0.011). No other biochemical or clinical differences were observed between these groups.

A critical sample cortisol level was associated with fast test nadir cortisol (R=0.574; p0.001) and Synacthen stimulated cortisol (R=0.448; p=0.004), but not with age (R=-0.009; p=0.922) or with glucose (R=0.025; p=0.802), insulin (R=-0.122; p=0.206) or GH (R=-0.163; p=0.088) levels measured in critical samples. Critical sample GH levels were inversely related to age (R=-0.322; p0.001) and measured glucose (R=-0.431; p0.001), but not to critical sample cortisol or height-SDS (R=0.021; p=0.836).

True cortisol deficiency was diagnosed in 4.3% (n= 8). Four had multiple pituitary deficiency. The other diagnoses were: primary adrenal insufficiency (n=1), IGF1 receptor mutation (n=1), fructose 1,6 diphosphatase deficiency (n=1) and transient hyperinsulinism (n=1).

Conclusions:

While an insufficient cortisol response to hypoglycemia is common among children, true cortisol deficiency is uncommon. As no one clinical parameter can diagnose cortisol deficiency, a Synacthen stimulation test should be performed to rule out adrenal insufficiency.

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Hepatocyte CB1 Receptor Regulation of Fatty Acid Oxidation and Steatosis: Metabolomics Insight

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Introduction:

The cannabinoid-1 receptor (CB1R) plays a crucial role in modulating fatty acid oxidation (FAO) and triglyceride (TG) uptake and accumulation in various tissues during obesity. However, the specific molecular mechanism governing these effects in the liver remains unknown. This study examines the impact of hepatocyte CB1R on FAO through the PPARγ/CD36/AMPK pathway, aiming to elucidate its significance in reversing obesity-induced steatosis.

Methods:

Wild type (WT) and hepatocyte-specific CB1R knockout mice ($LCB1^{-/-}$) underwent dietary interventions with standard and high-fat diets (STD and HFD, respectively), followed by treatment with the peripherally-restricted CB1R blocker (JD5037). Assessments included liver TG measurements, gene expression analysis, and FAO quantification. Nanostring and RNAseq were employed for gene expression profiling to identify downstream targets of hepatocyte CB1R. Additionally, comprehensive metabolomics and lipidomics analyses explored the profiles of polar metabolites and fatty acids, respectively.

Results:

Both $LCB1^{-/-}$ mice and their WT control counterparts showed comparable weight gain and increased hepatic TG levels on an HFD. JD5037 induced similar weight loss but significantly alleviated HFD-induced hepatic steatosis only in control mice, leaving hepatic TG content in $LCB1^{-/-}$ mice unaffected. Nanostring, RNAseq, and RT-qPCR revealed increased CD36 and PPARγ expression in obese animals, which were reversed by JD5037 in WT control animals. In $LCB1^{-/-}$, a smaller, non-significant upregulation of CD36 and PPARγ expression levels remained unaffected by JD5037. Hepatic AMPK activity, inhibited by CD36, decreased with HFD and was restored by JD5037 in WT mice, but remained largely unaffected in $LCB1^{-/-}$ mice. Consistent with changes in AMPK activation, HFD reduced liver FAO was reversed by JD5037 in WT mice, while in $LCB1^{-/-}$ mice, it remained unchanged. Prompted by the link between hepatocyte CB1R and FAO, lipidomics revealed 29 fatty acids mirroring CD36 expression and AMPK activity patterns. These findings collectively support the notion that increased FAO due to CB1R blockade diminishes the remaining tissue levels of fatty acids in obese WT mice. The lack of a similar reduction in fatty acid levels by JD5037 in the livers of $LCB1^{-/-}$ mice confirms the dominant role of hepatocyte CB1R in orchestrating this effect. Additionally, polar metabolomics highlighted a JD5037-independent reduction in glycolysis, supporting the shift to fatty acids as the primary energy source in obesity.

Conclusion:

Hepatocyte CB1R plays a pivotal role in modulating the FAO pathway, influencing hepatic TG content in obesity-induced steatosis. These findings highlight the potential therapeutic relevance of targeting hepatocyte CB1R to mitigate hepatic steatosis associated with obesity.

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Vitamin D down regulates Cytokines expression by the Immune system and its possible effect on Covid-19 disease

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Introduction:

Although the classical role of vitamin D is in Calcium regulation, recent studies emphasize its effects on other systems. It was shown already that vitamin D affect the immune system by moderating inflammation processes. Since Covid-19 patients are suffering from inflammation storm caused by the excess production of cytokines by the immune system, it is possible that vitamin D may contribute to the treatment of these patients.

Aims:

The purpose of the present study was to provide evidence for the anti-inflammatory activity of the active metabolite of vitamin D, namely,1,25-Dihdroxyvitamin D_3 ($1,25(OH)_2D_3$) and to shed a light on its mode of action.

Methods:

Human peritoneal Macrophages were obtained from effluent dialysates of patients in end-stage renal disease. Isolated Macrophages were incubated with vitamin D preparations, followed by LPS incubation. Protein levels of TNFα were determined by ELISA, and TNFα mRNA levels were determined by RT-PCR. Similar incubations were carried out on murine macrophage (P388D1) transfected cells with a reporter plasmid pNFkB-luciferase. Protein and mRNA levels of NFkB-p65, IkBα and of its phosphorylated form were evaluated.

Results:

It was found that $1,25(OH)_2D_3$, and its synthetic analog $1,24(OH)_2D_2$, downregulate the expression of TNFα in human macrophages, as well as in a murine macrophage cell line. Moreover, these results have elucidated the mode of action by which 1,25(OH)2D3 regulated the TNFα expression. It was found that both $1,25(OH)_2D_3$ and $1,24(OH)_2D_2$ increase the cytosolic IkBα that binds NFkB, and prevents its migration from the cytosol to the nucleus. NFkB is the main transcriptional factor for TNFα. Thus, inhibition of its migration to the cell nucleus reduces TNFα synthesis.

Conclusions:

The reduction in TNFα synthesis caused by the active metabolite of vitamin D may lead to moderation of the inflammatory storm developed in Covid-19 patients, and in other inflammatory diseases. These findings provide a biological basis and the mode of action by which vitamin D makes its impact on the Covid-19 disease. The present results emphasize the possible role of vitamin D in preventing Covid-19, or at least moderating its severity.

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Can lactation counseling at the end of pregnancy influence confidence in breastfeeding among women with pregestational diabetes?

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Background:

Women with pregestational diabetes mellitus (PGDM) face complex challenges when breastfeeding. Blood glucose management in addition to motherhood can cause emotional burden and many women report negative feelings when faced with both. Targeted interventions attempting to alleviate concerns and provide women with knowledge on what to expect are limited. The aim of this study was to evaluate whether targeted counseling towards the end of pregnancy can impact women's perceptions regarding breastfeeding.

Methods:

The data was collected as part of a prospective study that randomized women between 32-36 weeks gestation to receive either face to face instruction with a lactation consultant experienced in caring for women with diabetes versus women who received written handouts containing standard, non-diabetes-specific, breastfeeding instruction. All face-to-face instructions were conducted according to a uniform topic list by author TG, a certified lactation consultant, and lasted 30 to 60 minutes. Instruction content was based on a comprehensive literature review and TG`s experience, to include major topics known to influence breastfeeding for PGDM women. The purpose of the instruction was twofold: to elucidate practical aspects and strategies to overcome challenges of breastfeeding alongside diabetes, and to review realistic breastfeeding expectations for the early postpartum period. Data was collected via a structured questionnaire designed to evaluate attitudes and perceptions toward breastfeeding, provided before and after instruction.

Results:

Twenty-six women with PGDM received structured instruction. Women after instruction felt significantly more confident in their ability to manage blood glucose alongside breastfeeding (27% before vs 54% after instruction, p=0.048). More importantly, significantly more women felt confident in their breastfeeding knowledge (62% before vs 89% after instruction, p= 0.025). Although modestly, most other parameters the women were asked about also improved. Collectively, the instruction had a meaningful and positive impact on perception, opinions, self-perceived knowledge, and confidence to breastfeed alongside diabetes. Importantly, women also felt significantly more confident reaching out to healthcare professionals when needed (62% vs 89%, p=0.025), and not only social media or family and friends.

Conclusion:

A targeted counseling intervention at the end of pregnancy positively affected knowledge and confidence surrounding breastfeeding for women with PGDM. Further studies to find the optimal combination of education and support remain needed.

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Predicting factors for adverse outcomes of acute decompensated heart failure in diabetic patients hospitalized in internal medicine department

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Background:

Diabetes mellitus (DM) is common among patients admitted with decompensated heart failure (HF) and the presence of DM adversely affects the natural history of HF. The prognostic significance of DM on hospitalization outcomes of patients with acute decompensated HF (ADHF) remains inconclusive. Additionally, data are limited on what factors contribute to ADHF prognosis in diabetic patients.

Objective:

This work aimed to evaluate the predictive factors affecting the all-cause one-year mortality of diabetic patients with ADHF hospitalized in a department of internal medicine.

Methods:

This is analysis was done as part of a retrospective cohort study conducted to evaluate the clinical outcomes (length of hospitalization, in-hospital mortality, one-year overall mortality, and readmission rate within a year of follow-up) of patients with and without DM hospitalized for ADHF in the department of internal medicine A, at Kaplan Medical Center between 1/1/10 to 31/12/2019. Patients were categorized into diabetic and non-diabetic groups. Multivariable logistic regression was applied to study the association between the presence of diabetes and the all-cause one-year mortality while controlling for potential confounders. Confounders included demographic data (age, BMI, sex), and clinical data (such as treatment of HF, treatment of diabetes, duration of diabetes, glycemic control).

Results:

The final analysis involved 787 patients with ADHF, 491 patients had pre-existing DM. Diabetic patients were characterized by a higher prevalence of comorbidities (such as hyperlipidemia, obesity, and IHD), and a higher likelihood of smoking – all established risk factors for HF. Overall, among patients with diabetes, 108 (22%) died within a year of follow-up. The main risk factors identified that were significantly associated with mortality were older age, duration of diabetes (above and below 10 years), and duration of heart disease. Patients who died used significantly less angiotensin-converting enzyme inhibitors (ACEi) and Metformin (34% vs 53%, p-value 0.001 and 24% vs 39%, p value 0.004, respectively). Notably, the clinical outcomes of patients with diabetes were independent of glycemic control. In a multivariate analysis, only age and not using ACEi remained significantly associated with mortality in diabetic patients (OR=1.056, 95% CI 1.017-1.096, p=0.005) and (OR=0.494, 95% CI 0.250-0.978, p=0.043), respectively.

Conclusion:

Elderly diabetic patients hospitalized for ADHF had a poor long-term outcome. With the new era of disease-modifying therapies for HF, hopefully, these outcomes will improve.

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characterizing movement patterns of older individuals with type 2 diabetes in free-living environments using wearable accelerometers

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Background:

Type 2 Diabetes (T2D) is associated with reduced muscle mass, strength, and function, leading to frailty. This study aims to analyze the movement patterns (MPs) of older individuals with T2D across varying levels of physical capacity (PC).

Methods:

A cross-sectional study was conducted among individuals aged 60 or older with T2D. Participants (n = 103) were equipped with a blinded continuous glucose monitoring (CGM) system and an activity monitoring device for one week. PC tests were performed at the beginning and end of the week, and participants were categorized into three groups: low PC (LPC), medium PC (MPC), and normal PC (NPC). Group differences in MPs and physical activity were analyzed using non-parametric Kruskal–Wallis tests for both categorical and continuous variables. Dunn post-hoc statistical tests were subsequently carried out for pairwise comparisons. For data analysis, we utilized pandas, a Python-based data analysis tool, and conducted the statistical analyses using the scipy.stats package in Python. The significance level was set at p 0.05.

Results:

Participants in the LPC group showed lower medio-lateral acceleration and higher vertical and antero-posterior acceleration compared to the NPC group. LPC participants also had higher root mean square values (1.017 m/s2). Moreover, the LPC group spent less time performing in moderate to vigorous physical activity (MVPA) and had fewer daily steps than the MPC and NPC groups.

Conclusions:

The LPC group exhibited distinct movement patterns and lower activity levels compared to the NPC group. This study is the first to characterize the MPs of older individuals with T2D in their free-living environment. Several accelerometer-derived features were identified that could differentiate between PC groups. This novel approach offers a manpower-free alternative to identify physical deterioration and detect low PC in individuals with T2D based on real free-living physical behavior.

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Virtual reality`s impact on children with type 1 diabetes: a randomized cross-over trial on anxiety, pain, adherence, and glycemic control

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Objectives:

For children with type 1 diabetes (T1D), pain and needle phobia can cause postponing of changes in insulin pump infusion sets and continuous glucose monitors, and thus worsen glycemic control. We aimed to assess the effectiveness of virtual reality (VR) technology, in reducing pain and anxiety, and improving regimen adherence and glycemic control among children with type 1 diabetes (T1D).

Methods:

Children with T1D, managed with continuous glucose monitoring and insulin pumps, were recruited for a randomized cross-over trial. Children were randomized to one of two interventions for diabetes management: group 1 used VR glasses first and group 2 listened to vocal-guided affective imagery first (audio). After 1 month, the interventions were crossed over. The outcome measures included pain and anxiety assessment, regimen adherence, glycemic control, and patient-reported outcome measures (PROMs) of VR satisfaction and effectiveness.

Results:

Forty children, mean age 11.4 ± 1.8 years, participated. During the VR part, the monthly mean pain score compared to the baseline improved in both groups by 30% (p=0.03). A 14% reduction in the state anxiety score was observed from baseline to 1 month in both groups (p=0.009). Glycemic control measures including time in range, time above range, and glucose management indicator improved in both groups during the VR part (p0.004 for all measures), compared to the audio part. After one month, the patient-reported outcome measure (PROM) of satisfaction and effectiveness was 6-fold higher after 1 month in group 1 compared to group 2 (p=0.002). Regimen adherence improved for both groups.

Conclusions:

VR was shown to be effective in reducing pain and anxiety, improving regimen adherence, PROM, and glycemic control among children with T1D. We suggest incorporating VR technology in pediatric diabetes clinics to facilitate and improve coping and management of diabetes.

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Precision diabetes: identification and characterization of monogenic diabetes in a tertiary pediatric diabetes center in Israel

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Objectives:

Characterize individuals with monogenic diabetes (including maturity-onset diabetes of the young, MODY) in a tertiary pediatric diabetes center, and evaluate epidemiological, clinical, and biochemical risk factors.

Methods:

Medical records of all children aged 6 months to 18 years who were diagnosed with diabetes, between 2004 and 2022, were analyzed. A DNA sample was collected from children with negative pancreatic autoantibodies, a family history of diabetes, and/or atypical type 1 diabetes clinical presentation. Exome sequencing using a next-generation sequencing platform and comprehensive analysis of a monogenic diabetes gene panel were applied. The performance of the Exeter MODY probability calculator (MPC) score was assessed.

Results:

The cohort included 452 individuals, 160 (35.4%) had negative antibodies, and of them, 37 had a high clinical suspicion for MODY. Of the 37 samples sequenced, 27 individuals had a positive genetic result (21 pathogenic/likely pathogenic mutations, 6 variants of unknown significance), yielding a 73% genetic diagnosis rate. Most cases included mutations in GCK, HNF1A, and WFS, without any record of HNF4A. The median (IQR) age of diagnosis was 13.5 (10-16) years, with 81% female predominance in the positive diagnosis group compared to 30% in the negative group (p=0.006). The median Hba1c level at diagnosis was 1.3-fold higher in the positive group compared to the negative group (7% (6.2-8.4) vs. 5.5% (5.2-7.7), p=0.017). Five children (19%) in the positive group had a low (30%) MPC score and 7 (70%) in the negative group had a high (30%) MPC score. Therapeutic changes due to genetic results were made in 26 (70%).

Conclusions:

We describe a unique pattern of monogenic diabetes in a tertiary center in Israel. In cases of low MPC score with a high index of suspicion, genetic testing is warranted. High clinical suspicion is essential for early detection of monogenic diabetes and for optimizing precision medicine.

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The challenge of pre-operative radiological diagnosis of Appendiceal Neuroendocrine Neoplasms: Implications for Conservative Management of Acute Appendicitis

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Background:

In recent years, there is mounting evidence that antibiotic therapy is not inferior to surgery for non-perforated appendicitis in healthy patients. However, there is a small risk of missed appendiceal tumor. Appendiceal neuroendocrine neoplasms (ANEN) are the most common appendiceal tumor, occurring in approximately 1:200 appendectomies. Ninety percent of patients present with acute appendicitis, and ANEN is diagnosed in the surgical pathology review. Pre-operative imaging studies usually do not detect appendiceal tumors. The aim of this study is to identify radiological features that will distinguish ANEN from simple acute appendicitis, thus preventing the overlooking of an ANEN diagnosis at an early and curable stage.

Methods:

Data was extracted from a retrospective analysis database of 8,327 appendectomies from a tertiary medical center conducted during 2005-2018. Pre-operative Computerized Tomography (CT) or Ultrasound (US) scans of patients in the ANEN cohort and a random sample of patients with simple acute appendicitis were compared. Patients with other appendiceal tumors were excluded. All images were reviewed by a blinded, dedicated and experienced radiologist.

Results:

Of 62 ANEN cases in the cohort, 35 cases had pre-operative imaging studies available for analysis (20 CT, 15 US). The control group consisted of 50 cases with simple appendicitis (30 CT, 20 US). Age was similar between study groups (33.8±19.2 vs. 35.2±17.9, respectively, p=0.378), however female gender was more prevalent in the ANEN group (65.7% vs. 38.3%, p=0.017). ANEN size according to pathology report was 17.0±13.4mm, and mesoappendix invasion was evident in 37.1%. Pre-operative radiologic features were similar including appendiceal diameter, regional lymph node number and size. Evidence of solid tissue in the appendiceal lumen per CT scan was significantly more prevalent in the ANEN group compared to controls [7/20(35%) vs. 2/30(6.7%), p=0.0008].

Conclusions:

Although the majority of ANEN cannot be identified in pre-appendectomy imaging studies, 35% of cases demonstrate the presence of solid tissue in the appendiceal lumen. This finding may distinguish these patients from those with simple appendicitis and should lead to consideration of early surgical intervention, or close and more cautious surveillance if a conservative approach is selected. Radiologists as well as surgeons should be aware of the importance of this finding in patients with acute appendicitis.

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Glucose intolerance in pregnancy and risk of early-onset type 2 diabetes: a population-based cohort study

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Background:

The risk for type 2 diabetes (T2D) among women with glucose intolerance in pregnancy not meeting gestational diabetes criteria requires further investigation. We aimed to explore associations of various degrees of gestational glucose intolerance with the later risk of T2D.

Methods:

The national Israeli conscription database was linked to a nationally representative large health maintenance organization. Included were 177,241 women who were evaluated at adolescence and later underwent, during 2001-2019, two-step gestational diabetes screening with a 50-g glucose challenge test (GCT) using a threshold of 140 mg/dL, followed as needed by a 100-g oral glucose tolerance test (OGTT). The Carpenter-Coustan thresholds were used: at fast, exceeding 95 mg/dL; at 1-h, exceeding 180 mg/dL (10.0 mmol/L); at 2-h, exceeding 155 mg/dL; and at 3-h, exceeding 140 mg/dL. The primary outcome was T2D by 2021. Cox models were applied.

Findings:

During a median follow-up of 10.8 [5.2;16.4] years, 1,262 women were diagnosed with T2D. Crude incidence rates of T2D (per 10,000 person-years) were 2.6, 8.9, 26.1, and 71.9 among women with gestational normoglycemia, abnormal GCT with normal OGTT, one abnormal OGTT value (fasting or 1-h/2-h/3-h post-challenge), and gestational diabetes, respectively. Hazard ratios (HRs) for T2D in the three latter groups, compared to the gestational normoglycemia group, were 3.4 (95%CI, 2.8-4.2), 9.1 (95%CI, 7.6-10.9), and 24.8 (95%CI, 21.8-28.3), respectively, after adjustment for sociodemographic characteristics, adolescent BMI, and age at gestational screening. High fasting glucose modestly increased these hazards such that the adjusted HR for T2D in women with isolated elevated fasting glucose was 11.8 (95%CI, 8.6 to 16.3), and the adjusted HR in women with gestational diabetes and an abnormal fasting glucose was 38.0 (95%CI, 32.3-44.6).

The adjusted HRs, compared to women with gestational normoglycaemia, were 14.45 (95%CI, 12.2–17.16), 35.7 (95%CI, 29.7–42·99), and 61.2 (95%CI, 44.8–83.6) in women with gestational diabetes with two, three and four abnormal OGTT values, respectively. These findings persisted when models were further adjusted for number of glucose tests that were conducted during follow-up, or number of pregnancies.

Interpretations:

Gestational glucose intolerance, including conditions not meeting gestational diabetes criteria of the two-step strategy, has high risk for T2D. They should be recognized as risk markers for T2D, especially among women with abnormal fasting glucose. Equally important, women with GDM have markedly wide range of risk for type 2 diabetes that depends on the number of abnormal OGTT values, especially fasting glucose.

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Using point of care rapid cortisol measurement during adrenal venous sampling - a single center clinical experience

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Adrenal Venous Sampling (AVS) is the gold standard method to distinguish between unilateral and bilateral aldosterone secretion in patients diagnosed with primary aldosteronism. During the procedure, validating accurate sampling of the adrenal veins is critical in order to achieve clinically significant results. The recommended method to confirm correct sampling is by calculating selectivity index (SI), defined as adrenal to periphery cortisol ratio, yet laboratory cortisol results are usually available only after the procedure has ended, resulting in the need for re-sampling in another AVS session in case of failure.

Lately, Bnai Zion medical center applied a point of care rapid cortisol (RC) measurement done by iChroma test kit. RC is performed bedside at the catheterization room, enabling SI calculation within 15 minutes after blood sampling. Here we present our clinical experience with this method, which includes data of 14 AVS procedures done using RC, compared with 36 previous AVS procedures without RC. Validation of RC results and AVS success was determined by cortisol SI above 5 done by Cobas lab analyzer.

Using the RC method, AVS success rates improved from 67% to 79%. In two of the 14 cases (14%) low RC-SI ratio resulted in re-sampling during the same AVS session, leading to successful procedure. In one other case of low RC-SI results, repeated sampling during the same session did not succeed, sparing the need for repeated AVS session. Overall, rapid cortisol enabled us to avoid three (21%) repeated AVS sessions. In our cohort, SI ratio above 4.18 done by RC, correlated with 100% procedure success as validated by Cobas results, while lower values indicated failed sampling.

Our experience using RC, shows that RC measurement may help to improve AVS success rates and reduce the need for repeated AVS sessions. Prospective studies with larger number of cases are needed to validate these conclusions.

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CT-BASED SARCOPENIA ASSESSMENT: PREDICTING OUTCOMES IN ACUTE INFECTION PATIENTS

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Objectives:

In this retrospective cohort study, we investigated the prognostic value of sarcopenia evaluated by CT-based indices for adverse hospitalization outcomes in patients with acute infections.

Methods:

We analyzed data from 225 patients admitted to the hospital for acute infections between 2019 and 2020. Patients who had undergone an abdominal CT scan either up to one month before or within the first 3 days of hospitalization were included. Computed tomography image analysis was used to evaluate skeletal muscle mass (by skeletal muscle index- SMI) and muscle quality (by psoas muscle density, pMD).

Results:

Low pMD was associated with higher in-hospital mortality (31% vs. 11.4% p0.001) as well as higher longer-term mortality rates (p=0.008 for 30 days and 0.001 for 90- and 1-year mortality). Low pMD remained an independent poor prognostic factor after controlling for confounders, with an adjusted odds ratio (aOR) of 2.74, (95% CI 1.33-5.67, p=0.006) for 1-year mortality, and aOR of 2.61, (95% CI 1.23-5.55) for prolonged hospital stay. Low SMI was associated with adverse outcomes, although this association was not independent after controlling for confounders. Notably, patients with both low SMI and pMD exhibited the poorest hospitalization outcomes: aOR for 1-year mortality 5.015 (95% CI 1.767-14.23, p=0.002), and prolonged LOS aOR 3.197, (95% CI 1.159-8.821, p=0.025).

Conclusions:

CT-based muscle indices serve as independent prognostic factors in medical patients admitted with acute infection. Incorporating radiological assessments of sarcopenia into routine care for hospitalized patients with acute infection may enable risk stratification and early intervention in reversible conditions.

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Methimazole for Prevention of Iodinated Contrast Media Induced Exacerbation of Thyrotoxicosis in Susceptible Patients

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Introduction:

The role of anti-thyroid therapy with methimazole for prevention of iodinated contrast media (ICM) induced thyrotoxicosis is unclear. The aim of the current study was to investigate the efficacy of methimazole in prevention of thyrotoxicosis in patients undergoing ICM imaging or procedures.

Methods:

Retrospective cohort study, performed at Rabin Medical Center, included patients ≥18 years admitted to the hospital, underwent ICM imaging or procedure, and treated with methimazole prior to exposure.

Results:

A total of 179 patients with 202 hospitalizations were included. Mean age was 72.3±13.5 years, 64% female. Nearly all patients (99%) had history of thyroid disease and 91% were treated with methimazole prior to admission. Seventy-five patients had low TSH prior to ICM exposure. In this high-risk group, methimazole led to normalization of TSH after discharge in 19%, and 64% remained with low TSH but with a small median difference in FT4 of -0.5, IQR (-5.9)-(5.2). In eight patients with dose increase during hospitalization, treatment with methimazole was beneficial with median FT4 decrease of -6.2, IQR (-9.2)-(-1) and TSH increase of 0.2, IQR 0.02-0.7. In 110 patients with normal TSH before admission, 71% remained euthyroid after discharge, 13% had low TSH and 9% had high TSH. In 15 patients with high TSH before admission, only two normalized TSH, 47% remained with high TSH, and 27% had low TSH after discharge.

Conclusion:

In patients receiving methimazole before ICM exposure, thyroid functions remained stable without exacerbation of thyrotoxicosis. Furthermore, in patients with low TSH levels before admission, increasing dose of methimazole before iodine exposure led to improvement in thyroid functions after discharge.

Fib-4 score is a Prognostic Predictor of End-Stage Liver Disease: A Nationwide Retrospective Study

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Background:

Non-alcoholic fatty liver disease (NAFLD) is highly prevalent and underdiagnosed among people with or without metabolic syndrome. Only a small fraction of the population develops liver specific morbidity and mortality. Identifying those who are at risk for end stage liver disease presents a significant clinical challenge. FIB-4 score is a non-invasive fibrosis scoring system recommended for risk stratification in people with chronic liver disease. The aim of the study was to assess whether FIB-4 score is an independent predictor of hard clinical outcomes of cirrhosis and its complications in the general population.

Methods:

This retrospective study was conducted using Clalit Health Services' national database. Included were adults with a calculated FIB-4 score between 2005 to 2020. People who ever had a diagnosis of liver metastasis or chronic liver disease, other than NAFLD, were excluded from the study. The primary outcome event was the first diagnosis of cirrhosis, cirrhosis related complication (liver failure, esophageal varices) or hepatocellular carcinoma (HCC), using a validated set of ICD and procedure codes. The association between FIB-4 score and liver specific events was analyzed using a cox-model.

Results:

Among 2.36 million people, with a median follow up of 13.0 years, 5061 (0.2%) people developed an end-stage liver disease. Among those, 2,554 (50.5%) developed hepatic failure, 1,408 (27.8%) developed HCC, and 1,021 (20.0%) presented with esophageal varices. The median time for the first diagnosis was 7.0y (IQR: 3.3-10.8). FIB-4 score $\geq$ 1.3 was an independent predictor of the primary outcome, HR 1.99 (95% CI 1.86-2.13). Additional predictors were male sex, advanced age, type 2 diabetes, type 1 diabetes, and BMI.

Conclusion:

FIB-4 score at baseline is an early independent predictor of end stage liver disease, most likely related to NAFLD, in the general population.

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Subclinical Hypothyroidism in Elderly Patients Hospitalized in Acute Medical and Surgical Wards

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Context:
Hypothyroidism is a common condition in the elderly, affecting 5–20% of women and 3–8% of men. Subclinical hypothyroidism (SCH) is defined as a modestly elevated TSH level, up to 10mIU/l, with peripheral T4 and T3 levels within the normal range. The estimated prevalence in the general population ranges between 3 and 8%. There is evidence for a link between an element of hypothyroidism and longevity.

Objective:
To examine thyroid function, and specifically subclinical hypothyroidism, in elderly patients hospitalized in acute medical and surgical wards, with respect to age and gender.

Subjects and Methods:
Retrospective analysis of thyroid function tests from the hospital laboratory database from the years 2012 to 2020 inclusive. Patients aged 65 or over and hospitalized in the acute medical or surgical surgical wards with a TSH result were included, the first result during the study period being used for analysis together with FT4 results where available. Subjects were divided into groups according to TSH result (Low, Normal, SCH and High) and by age group (Youngest Old 65-74, Middle Old 75-84, Oldest Old 85-100 and Centurion over 100).

Results:
Altogether 16100 results were obtained, 7258 (45%) from men and 8842 (55%) from women. TSH increased across age groups, and was slightly higher in women than men in each group. Comparing the Normal and SCH groups, there was no significant difference in FT4 values across groups, 1.17 vs 1.14 ng/ml, pairwise t-test with correction for multiple comparisons p=0.22. Examining the distribution of subject with TSH in the SCH range revealed a clear preponderance in women compared to men. Comparison across age groups revealed a steady increase with age, apart from a decrease in the Middle Old woman, and particularly in the Centurion group, with the sex difference clear in each age group.

Mean TSH (N)	Youngest Old	Middle Old	Oldest Old	Centurion
Men	1.94 (2807)	1.99 (2793)	2.17 (1820)	2.80 (25)
Women	2.19 (2537)	2.20 (3524)	2.48 (2903)	1.96 (45)

% with SCH	Youngest Old	Middle Old	Oldest Old	Centurion
Total	6.5	6.5	7.8	12.8
Men	4.8	5.4	5.8	12.0
Women	8.5	7.4	9.1	13.3

Conclusions:
Examining thyroid function tests in a hospitalized population aged 65 or older we have confirmed a rise in TSH with age, with higher values in women than men. The proportion of subjects with SCH also rises with age and is strikingly high in the Centurion group. We suggest that these results support the proposition that an element of hypothyroidism may actually improve survival. A strength of our study is the large number of subjects, while a weakness is the lack of clinical data such as underlying illness or treatments.

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Safety of SGLT2 inhibitors in kidney transplant recipients with diabetes mellitus

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Background:

Kidney transplant recipients (KTR) with diabetes mellitus are at risk for developing cardiovascular and renal complications. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) may delay or prevent these outcomes in KTR, however, robust data on their efficacy and safety in KTR is lacking. One of the main reasons for the underuse of SGLT2i in KTR might be the fear of serious adverse events in this special population, including acute kidney injury (AKI), euglycemic diabetic ketoacidosis (DKA) and urinary tract infection (UTI).

Methods:

A retrospective cohort study comparing KTR with diabetes mellitus treated with SGLT2i (SGLT2i group) and KTR with diabetes mellitus who were treated with other anti-hyperglycemic agents (control group). Data were collected from electronic medical records of patients who were being followed at Rabin Medical Center, Israel. Primary safety outcomes were: (1) a renal-related composite outcome of dialysis, re-transplantation, acute kidney injury (AKI) or acute rejection and (2) hospital admission due to urinary tract infections (UTIs). Secondary safety outcomes were: each component of the primary outcome separately, the occurrence of DKA, and a composite of dialysis, re-transplantation, AKI, acute rejection or all-cause mortality.

Results:

Two hundred and forty patients were included in each group, (20% women, median age 63 and 64 years in the control and SGLT2i group, respectively; maximum follow-up 3 years). The composite outcome of dialysis, re-transplantation, AKI or acute rejection occurred less in SGLT2i users (8.9 vs. 13.3 events/100 patient-years, HR 0.66, 95% CI 0.45-0.98, p=0.037); however, after adjustment for independent predictors the risk was similar between the groups (HR 0.99, 95% CI 0.65-1.52, p=0.970). Similar results were seen in a composite outcome of dialysis, re-transplantation, AKI, acute rejection and mortality. The incidence of hospital admissions due to UTIs was 5.7 versus 10.5 events/100 patient-years in SGLT2i users compared to the control group (HR 0.53, 95% CI 0.33-0.85, p=0.007). DKA occurrence was negligible and similar between the groups. Mortality rates were 3.9/100 person-years in SGLT2i users compared to 9.3/100 person-years in non-users (unadjusted HR 0.43, 95% CI 0.26-0.72; adjusted HR 0.66, 95% CI 0.38-1.14, p=0.135).

Conclusion:

No increased adverse renal-specific outcomes were seen in KTR with diabetes mellitus treated with SGLT2i, nor did adverse outcomes such as UTIs or DKA. SGLT2i therapy seems safe to use in KTR with diabetes mellitus. RCTs are needed in this population to solidify our retrospective results.

SGLT2 inhibitors show cardiovascular benefit in kidney transplant recipients with diabetes mellitus

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Background:

Type 2 diabetes mellitus (T2DM) poses an increased cardiovascular (CV) risk as well as high risk for chronic kidney disease. Kidney transplant recipients (KTR) with diabetes mellitus are at even higher risk for developing CV events. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) were proven to decrease the risk for major adverse CV events (MACE), as well as CV mortality in large randomized controlled trials. Nevertheless, KTR were excluded from these studies. Hence, we aimed to assess the CV effects in KTR with diabetes mellitus.

Methods:

We performed a retrospective cohort study comparing KTR with diabetes mellitus treated with SGLT2i (SGLT2i group) and KTR with diabetes mellitus who were treated with other anti-hyperglycemic agents (control group). Data were collected from electronic medical records of patients who were being followed up at Rabin Medical Center, Israel. The primary outcome was a composite of acute coronary syndrome (ACS), stroke/transient ischemic attack (TIA) or all-cause mortality. Secondary outcomes included each of the primary outcomes separately, and a composite outcome of congestive heart failure or all-cause mortality.

Results:

Two hundred and forty patients were included in each group, (20% women, median age 63 and 64 years in the control and SGLT2i group, respectively; maximum follow-up 3 years). 45% had a history of ischemic heart disease and 21% had cerebrovascular disease prior to initiation of SGLTi treatment (versus 42% and 16%, respectively, in matched control, p0.05). The incidence of ACS, stroke/TIA or all-cause mortality was 7.9 compared to 13.6 events/100 person-years (adjusted HR 0.64, 95% CI 0.42-0.97, p=0.039). The number of events per 100 person-years of congestive heart failure or all-cause mortality was lower in SGLT2i users (5.7 compared to 11.6), although the incidence of this composite outcome was similar between the study groups after adjustment to other independent predictors (HR 0.82, 95% CI 0.50-1.32, p=0.410).

Conclusions:

KTR patients with diabetes mellitus who are treated with SGLT2i seem to have MACE benefit similar to non-transplant patients with diabetes mellitus. Special consideration should be taken into account in this special population due to safety concerns, however, the benefit may be even more robust due to the high CV risk of these patients.

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The Relationship Between Nutrition Knowledge and Dietary Adherence among Adults with Type 2 Diabetes

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Introduction:

Medical Nutritional therapy is one of the cornerstones of diabetes therapy and self-management. Dietary intervention and diabetes education programs aim to increase patients' dietary knowledge to promote patient adherence to dietary recommendations. Eating behaviour is a complex interplay of physiologic, psychological, socioeconomic, and genetic factors. It is not known, to what extent patient education predicts dietary adherence. The aim of our study was to assess the relationship between nutrition knowledge and adherence to dietary recommendations among patients with type 2 diabetes.

Methods:

A total of 134 patients with T2DM from the diabetes clinic in a single hospital in Israel were enrolled for an interviewer-administered survey. Dietary adherence to mediterranean diet, which is culturally well accepted in Israel and advocated by professional diabetes guidelines, was measured by the I-MEDAS questionnaire. Dietary knowledge was quantitively assessed using a questionnaire adapted for locally available foods. Additional clinical and anthropometric characteristics were retrieved from the patients' electronic medical record. The relationship between knowledge in nutrition and dietary adherence was analysed using logistic regression analyses.

Results:

The average age of the patients was 70±10.7. 54.5% were women, with 1.33±1.12 diabetes-related complications. 40% were treated with insulin, and the average A1C was 7.1±1.1 %. Overall, the average Knowledge score was 12.1±2.4 (score 0-17), and the average adherence score was 11.0± 2.1 (score 0-17). In Multivariate logistic regression, there was a positive correlation between nutritional knowledge and dietary adherence. People in the highest tertile of knowledge in nutrition were more than 4 folds more likely to have dietary adherence score in the highest tertile (beta coefficient 4.6, 95% CI 1.5-14.8, p=0.01), compared to people in the lowest tertile of knowledge. Of note, the overall predictive performance of the regression model was poor (R2 = 0.10, p0.05).

Conclusion:

Nutritional knowledge is a predictor of dietary adherence in patients with type 2 diabetes. Our results are limited by the small size and relatively homogenous sample of patients. The large unexplained variance in dietary adherence might be related to parameters other than dietary knowledge, such as behavioral traits or environmental setting, which were unaccounted for in this study.

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Muscle-to-fat ratio in children and adolescents with type 1 diabetes in predicting glycemic control and partial clinical remission

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Background:

Advances in treatment could mitigate the expected adverse changes in body composition of children and adolescents with type 1 diabetes (T1D).

Objectives: To examine the evolutions of weight status and body composition and their association with glycemic control and partial clinical remission in youth with T1D.

Methods:

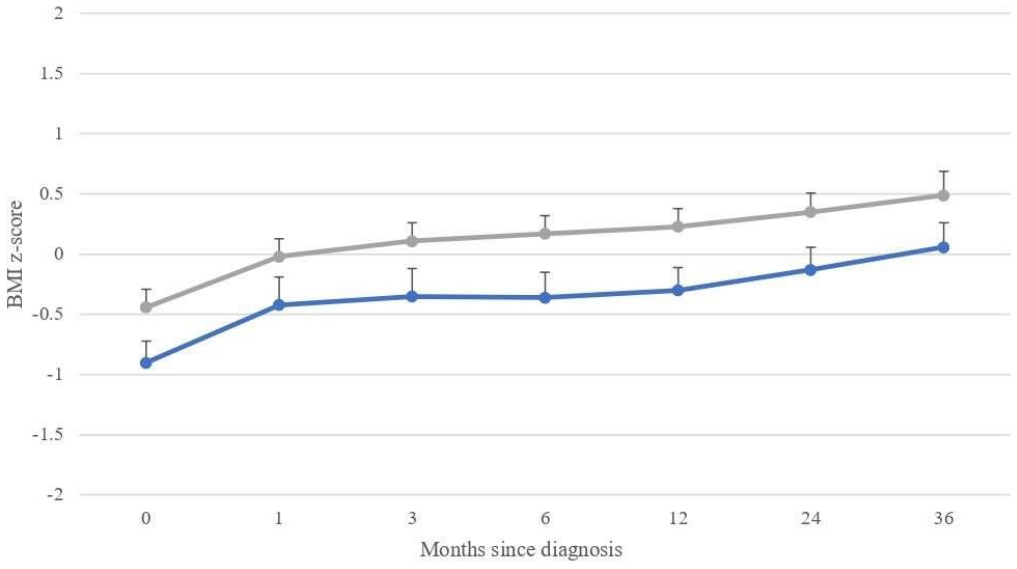
Ninety-nine subjects with T1D (median age 9.5 [IQR 7.3,12.9] years, 59.6% boys) were longitudinally followed for three years since diagnosis. Data at seven pre-determined time points were extracted from medical files. Outcome measures included body mass index (BMI) z-scores, muscle-to-fat ratio (MFR) z-scores, hemoglobin A1c (HbA1c) levels, continuous glucose monitoring metrics, and insulin dose-adjusted HbA1c (IDAA1c) levels.

Results:

The BMI z-scores increased significantly (p 0.001) for both sexes, with no significant change in MFR z-scores over time. The girls had higher BMI z-scores (p 0.001) and lower MFR z-scores than the boys (p = 0.016). The mean HbA1c levels decreased during the first month and at 3 months since diagnosis (p 0.001), then plateaued and achieved a median overall HbA1c of 7.1% for the entire cohort. At 12 months, 37 participants (37.6%) were in partial clinical remission, as evidenced by IDAA1C ≤9. The odds of partial clinical remission at two years increased by 2.1-fold for each standard deviation increase in the MFR z-score (p 0.001). Higher MFR z-scores were associated with better metabolic control.

Conclusions:

Integration of body composition assessments could mitigate adverse body changes in pediatric patients with T1D.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BMI z-score
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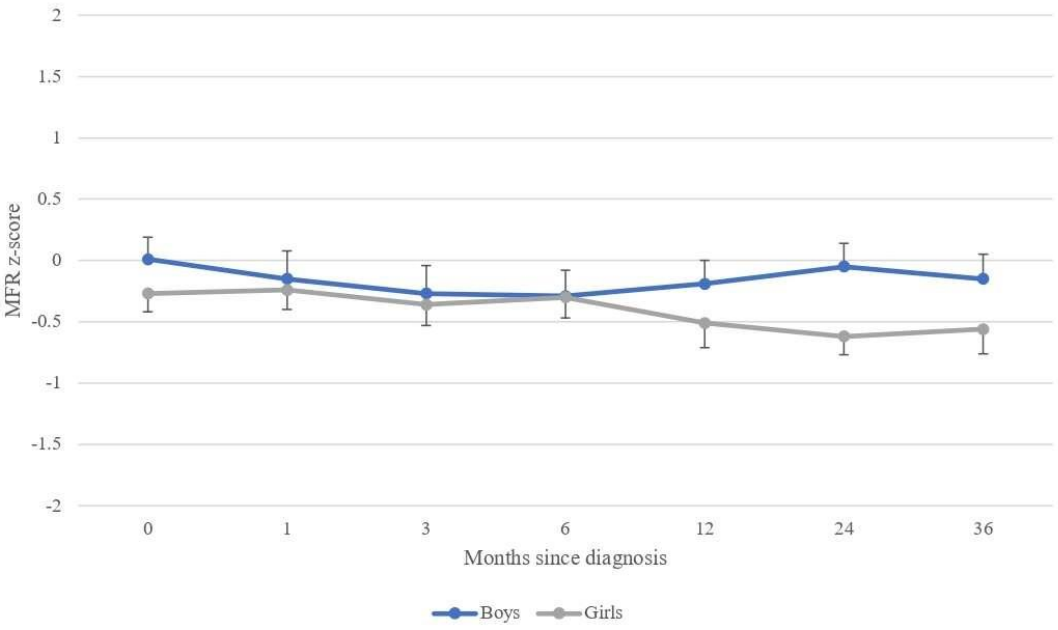
Months since diagnosis
Boys
Girls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Boys
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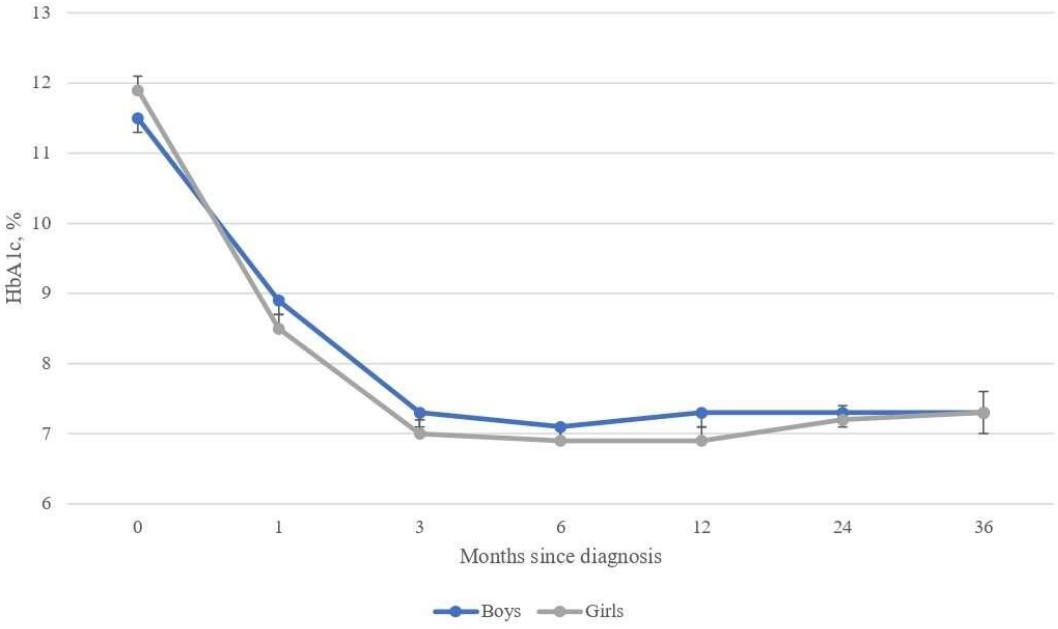
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10
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HbA1c, %
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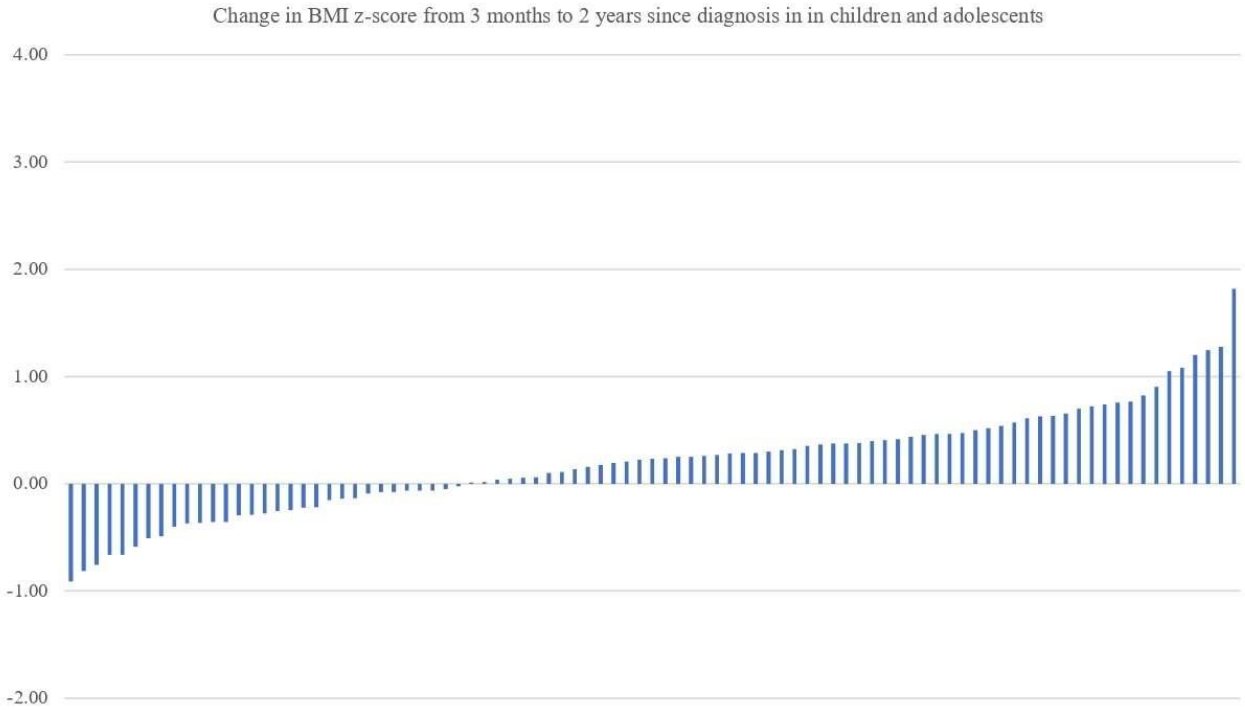
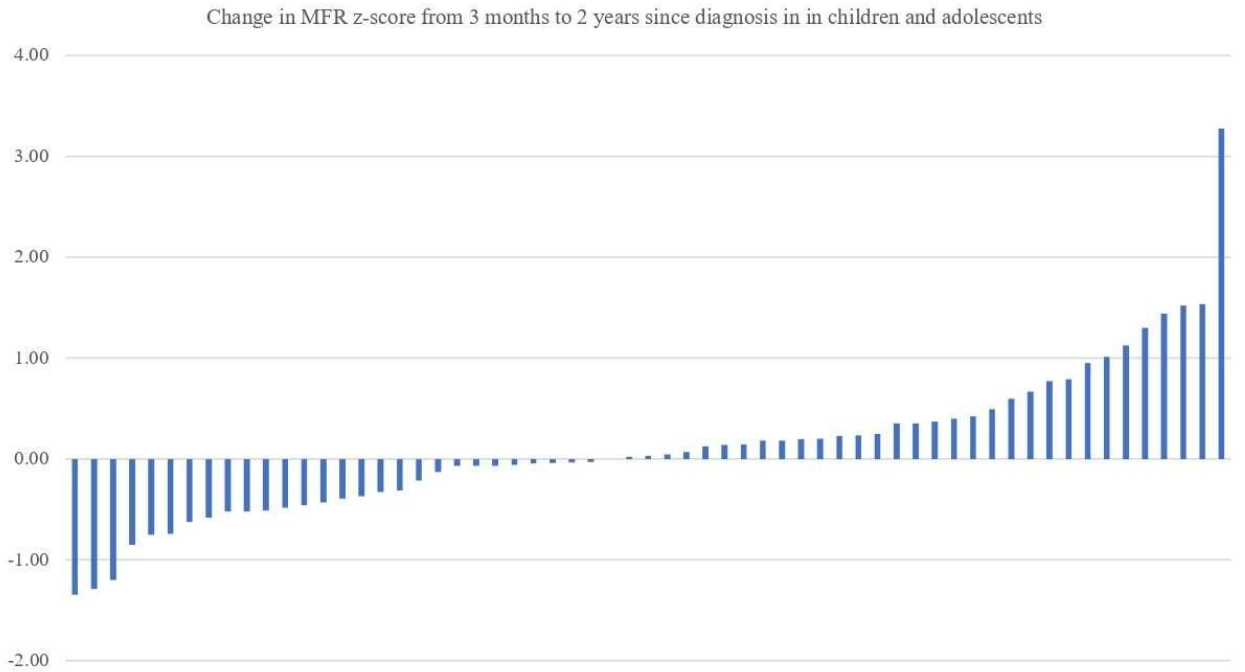
36
Months since diagnosis
Boys
Girls

0.001). Girls had significantly higher BMI z-scores than boys (psex 0.001). (B) MFR z-scores presented as the mean and SEE. Boys had significantly higher MFR z-scores than girls (psex = 0.016), but there was no significant change over time for both sexes (ptime 0.05). (C) HbA1c levels presented as the mean and SEE. The graph demonstrates a significant decrease in HbA1c levels from baseline to one month and three months, followed by a plateau (ptime 0.001). There were no significant sex differences (psex 0.05). The results for the boys are shown in blue and those for the girls in grey." width="1065" height="1881"





181

The Estrogen Receptors and ARE/Nrf2 are Involved in Protecting Human Dermal Fibroblasts from Damage Caused by Mitochondrial Disfunction

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Skin ageing is influenced by several factors including environmental exposure and hormonal changes. Reactive oxygen species (ROS), which mediate many of the effects of these factors, can be formed by extrinsic factors, such as sun exposure, or can result from mitochondrial dysfunction as occurs during ageing. Several studies have shown the protective role of estrogens on skin health. The aim of the current study was to examine the damage to dermal fibroblasts by mitochondrially generated ROS, and to study the mechanism of the protective effects of estradiol. Rotenone, a complex I inhibitor, was used to cause mitochondrial dysfunction in human dermal fibroblasts and its effects on mitochondrial and cytosolic ROS levels, mitochondrial respiration, cell death, apoptosis, matrix metalloproteinase-1 (MMP1) and pro-collagen secretion were determined as markers of skin damage. Rotenone caused substantial reduction of respiration, followed by increased mitochondrial and cytosolic ROS which resulted in apoptotic cell death, increased MMP1 secretion and decreased collagen secretion. Pretreatment with estradiol recovered more than 50% of the respiratory activity, reduced mitochondrial and cytosolic ROS levels and MMP1 secretion and increased cell number and collagen secretion. These effects can be partially explained by a cooperative effect of estradiol and rotenone on Antioxidant Response Element (ARE/Nrf2) transcriptional activity, which leads to upregulation of antioxidant proteins such as NQO1 and Trxr1. To determine if estrogen receptors (ER) are involved in the protective effects, we used the ER inhibitor, Fulvestrant. This inhibitor, which completely inhibited ER Response Element reporter activity, partially prevented the protective effects of estradiol. The protective effects of estradiol were Similarly reduced by ML385 and Ochratoxin A, that are inhibitors of the ARE/Nrf2 transcription system. Incubating the cells with Fulvestrant and Ochratoxin A, which inhibit both pathways, completely blocked the protective effect of estradiol. These results suggest that the estrogen receptors and the ARE/Nrf2 signaling pathways are involved in the protective effects of estradiol against the damage caused by rotenone-induced mitochondria generated oxidative stress.

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ER stress-induced neonatal diabetes: Effects of glucotoxicity on β-cell function and diabetes

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Introduction:

Prolonged exposure to hyperglycemia induces β-cell dysfunction (glucotoxicity), and aggravates type 2 diabetes (T2D). Whether this is true also in neonatal diabetes induced by proinsulin gene mutations is not known. SGLT2 inhibitors (SGLT2i) like dapaglifozin reduce hyperglycemia by inducing glycosuria. We studied the effects of dapagliflozin on β-cell function, ER stress and inflammation in Akita mice, which develop severe hyperglycemia and insulin deficiency at young age due to a missense mutation in Ins2 gene, resulting in irreparable proinsulin misfolding and consequently "extreme" β-cell ER stress, mimicking neonatal diabetes and T1D in humans.

Methods:

Akita mice were treated with dapagliflozin (10 mg/kg in drinking water) for 2-6 weeks starting post weaning at onset of hyperglycemia. Glucose tolerance was assessed by intraperitoneal glucose tolerance test (IPGTT) at 2 and 6 weeks after 48 h drug washout. Proinsulin and insulin content and secretion were analyzed by ELISA. The expression of proinsulin, insulin, the β-cell transcription factors PDX-1 and Nkx6.1 and the stress markers BiP and TXNIP were assessed by immunofluorescence. The genetic signature in islets of Akita mice treated with or without dapagliflozin compared to wildtype mice (WT) was analyzed by RNA-seq.

Results:

Treatment of diabetic Akita mice with dapagliflozin followed by drug washout leading to complete elimination of the drug (confirmed by LCMS), improved glucose tolerance, most prominently at 6 weeks. In Akita mice, pancreatic insulin content was decreased by ~74.4%, whereas treatment with dapagliflozin induced 2- and 2.5-fold increase in insulin and proinsulin content, respectively, without affecting proinsulin/insulin ratio. There was a small decrease of PDX-1 and Nkx6.1 expression, which was partially prevented by dapagliflozin. In addition, dapagliflozin decreased the expression of stress markers BiP and TXNIP. Multiple genes involved in the regulation of exocytosis were downregulated in Akita islets and restored by dapagliflozin. GSEA showed that genes involved in unfolded protein response (UPR), DNA damage repair, mTORC1, autophagy and inflammation were enriched in Akita compared to WT islets. Treatment with dapagliflozin downregulated the expression of inflammatory genes, including T- and B-cell receptor signaling and TNFα via NFκB signaling, without affecting UPR gene expression.

Conclusions:

In ER stress-induced neonatal diabetes, dapagliflozin induces sustained improvement of diabetes and β-cell function, despite persistent proinsulin misfolding/ER stress. Improved β-cell function is mainly explained by recovery of proinsulin synthesis and increased expression of genes regulating exocytosis, with minor effects on β-cell differentiation. In addition, SGLT2i alleviates islet inflammation, which may contribute to amelioration of β-cell function.

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Unveiling the spectrum of mitochondrial diabetes – a single center, multidisciplinary case series analysis

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[2]*Faculty of Medicine, Tel-Aviv University*

[3]*Neurologic ward, Shamir medical center*

Introduction:

Mutations in mitochondrial DNA are rare etiologies of adult-onset diabetes mellitus (DM). The most common form of mitochondrial diabetes found in the MT-TL1 (m.3243ANG) genotype, manifesting clinically as maternally inherited diabetes and deafness (MIDD) or mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS). The key abnormality causing DM is inefficient and suboptimal glucose-stimulated insulin secretion. Treatment of mitochondrial diabetes with metformin therapy is generally avoided due to the high risk of lactic acidosis. There is little published evidence specific to mitochondrial diabetes to guide pharmacologic treatment, with few cases published on mitochondrial diabetes and newer agents.

Aim:

To better define and understand the natural history of mitochondrial diabetes.

Results:

We present 4 patients with diabetes mellitus and 1 patient with impared fasting glucose (IFG) from the 10 patients who were treated in a multidisciplinary clinic for MELAS patients in Shamir medical center during the past year. Mean age of DM diagnosis was 38.5 years and mean age of MELAS diagnosis was 47.4 years. 2 patients were diagnosed as type 1 DM despite negative anti GAD antibody test, and patients 2 were diagnosed as type 2 DM. 2 patients are treated with multiple daily insulin injections and are connected to Libre freestyle continous glucose monitoring device. 1 patient is treated with GLP1 agonist weekly injections and sulfalylurea daily, 1 patients is treated with an SGLT2 inhibitor, and the IFG patient is treated with only diet and lifestyle changes. 2/5 patients developed lactic acidosis under past Metformin treatment. No patient suffered from DKA or severe hypoglycemia. The current mean HBA1C level is 7.4% . 1 patient has microvascular complications (neuropathy and nephropathy), and no patient has macrovascular complications. 2/5 patients suffer from overweight, 2/5 from dyslipidemia, and 1/5 from hypertension. Other MELAS manifestations are hearing loss in 4/5 patients, neurological in 1/5 patients, cardiologic in 2/5 patients.

Conclusion:

Mitochondrial diabetes is a rare form of diabetes with little published experience about natural history and treatment options. Diagnosis of DM usually preceds MELAS diagnosis which may lead to inappropriate medical tretment and complications. Our multidisciplinary clinic for MELAS patients will enable to better define, understand and treat patients with mitochondrial diabetes.

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Polyethylene Glycol Thyroid-stimulating Hormone (PEG-TSH) Testing in the Management of Pediatric Thyroid Dysfunction

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[1]*Pediatric Endocrinology, Dana-Dwek Children's Hospital*

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

[3]*The Endocrine Laboratory, Tel Aviv Sourasky Medical Center*

Purpose:

The polyethylene glycol (PEG) methodology is used for investigating incongruities in laboratory assays, such as thyroid-stimulating hormone (TSH) measurements. The aim of the study is to investigate the practical application of PEG-TSH testing in cases of discrepancies between elevated TSH and normal free thyroxine (FT4) levels.

Methods:

A real life observational study conducted in a tertiary medical center. The hospital's electronic database was queried for TSH tests performed in pediatric patients between 2015 and 2023. Of those, PEG-TSH were identified. Patients` clinical and biochemical characteristics and PEG-TSH-guided management were assessed.

Results:

In total, 2949 TSH tests were performed in 891 children and adolescents for various indications. Among them were 61 (2.1%) PEG-TSH results, mean age 7.1 ± 5.3 years, of 38 patients (4.3%) comprised of 16 with congenital hypothyroidism, 16 with subclinical hypothyroidism, and 6 with Hashimoto thyroiditis. Both the TSH and the PEG-TSH levels of patients with congenital hypothyroidism were higher than those of the other two groups (P=0.021 and P=0.009, respectively), with no group differences in FT4 levels. Spearman's correlation analysis revealed a strong association between TSH and PEG-TSH levels: r=0.871, P0.001. In nearly one-half of the cases, clinical decisions made by clinicians (decreasing the dose or not initiating L-thyroxine treatment) were affected by the PEG-TSH results.

Conclusion:

Our findings support PEG-TSH testing for determining appropriate TSH levels and avoid unnecessary thyroid hormone treatment among children and adolescents. We propose the suitability of managing their clinical condition based upon age-appropriate clinical parameters and FT4 levels when their PEG-TSH levels are within the normal range.

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Unraveling the Homeostasis of Gastric Neuroendocrine Cells: Insights from Single-Cell RNA Sequencing, Transgenic Mouse Models and Human Organoids

Amit Elad[1], Dr. Rachel Schyr[1], Mrs. Haya Ben-Hayun[1], Mrs. Deborah Durand[2], Mrs. Michelle Malis[1], Mr. Mohamed Abo-Tanha[1], Mr. Doron Kleiman[1], Mr. Botros Moalem[1], Mr. Moshe Pashkus[1], Mrs. Tamar Harats[1], Mrs. Dana Sender[1], Mrs. Dana Orzech[1], Dr. Sharona Tornorvski[3], Dr. Shira Anzi[1], Dr. Yael Riahi[4], Dr. Ariel Benson[5], Dr. Ronit Grinbaum[6], Dr. Esther Forkosh[5], Dr. Yuval Yishai[5], Dr. Liron Birimberg-Schwartz[2], Dr. Myriam Grunewald[2], Prof. Danny Ben-Zvi[1]

[1]*Faculty of Medicine, Department of Developmental Biology and Cancer Research, Hebrew University of Jerusalem, Israel*

[2]*Hadassah Organoid Center, Hadassah-Hebrew University Medical Center, Israel*

[3]*Faculty of Medicine, Department of Immunology and Cancer Research, Hebrew University of Jerusalem, Israel*

[4]*Endocrinology and Metabolism service, Hadassah-Hebrew University Medical Center, Israel*

[5]*Institute of Gastroenterology and Liver Diseases, Department of Internal Medicine, Hadassah-Hebrew University Medical Center, Israel*

[6]*Department of Surgery, Hadassah-Hebrew University Medical Center Mount Scopus, Israel*

Neuroendocrine cells (NECs) in the respiratory and gastrointestinal tracts are important in coordinating systemic functions. We focused on gastric-NECs which mainly include ghrelin-secreting X-cells and histamine-secreting enterochromaffin-like-cells (ECLs) in the corpus, and gastrin-secreting G-cells and serotonin-secreting enterochromaffin-cells (ECs) in the antrum. We used single-cell RNAseq (scRNAseq) of human tissues, transgenic mouse models and human organoids to study the differentiation and turnover of these cells and characterize their transcriptional profiles.

We found that ECLs may express genes coding for several neuropeptides/hormones including Neuropeptide-W, Spexin, Enterostatin, Luteinizing-Hormone and TPH1, the rate-limiting enzyme in serotonin production indicating potential secretion of both histamine and serotonin, while Bona fide ECs are rare in the corpus. Correspondingly, 16% of corpus NECs were positive for serotonin Immunostaining. X-cells express the histamine and Glp1 receptor genes, suggesting a direct effect of these hormones. The rare gastric L-cells of the corpus were found to express the genes for glucose-transporter SGLT1 and PC1-convertase, which is necessary for GLP1 biosynthesis. Surprisingly, these cells express other satiety-related hormones such as PYY, UCN3 and CCK.

The differentiation of pancreatic, intestinal and colon NECs requires the expression of transcription factor (TF) NGN3, while the TF ASCL1 is essential for pulmonary NEC development. Our analysis shows that antral NECs is driven by both ASCL1 and NGN3, while corpus NECs are only ASCL1-driven. This finding suggests that anterior-posterior position of endodermal tissues drives NEC differentiation program, rather than their affiliation to the respiratory or GI systems. We discovered that PTF1A, a TF important for pancreatic and neuronal development, is important for ECL differentiation downstream of ASCL1. Ptf1a-KO neonate mice are devoid of ECLs while sparing other gastric-NECs.

We utilized Ptf1a-CreER mice to study corpus NEC turnover. Nine months-long pulse-chase revealed the unexpected survival of approximately half of the ECLs and X-cells. This finding challenges the conventional understanding of rapid turnover of intestinal NECs, and suggests resemblance to pancreatic or pulmonary NECs.

Finally, after identifying conditions that drive gastric-NEC differentiation we developed the first adult-derived human corpus organoid model featuring gastric-NECs. Currently, we utilize this model to map signals and TFs governing gastric-NEC differentiation and maturation, employing pharmacological interventions and AAV-mediated TF overexpression.

In conclusion, our study unveils the distinct characteristics of gastric-NECs and challenges paradigms regarding their differentiation, turnover rate and roles. The results establish foundations for the developmental genetics of gastric-NECs, with implications in NEC tumor biology, gastric biology and metabolic homeostasis of the organism.

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Changes in Weight and BMI Following Treatment for Cushing Syndrome: Long-Term Outcomes and Potential Predictors

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[1]*Tel Aviv University, Sackler School of Medicine, Tel Aviv, Israel*

[2]*Rabin Medical Center, Beilinson Hospital, Institute of Endocrinology, Petach Tikva, Israel*

[3]*3Rabin Medical Center, Beilinson Hospital, Research Authority, Petach Tikva, Israel*

Background:

In patients presenting with Cushing syndrome (CS), weight and total body fat are higher than matched controls. We aim to assess the changes in weight and body-mass index (BMI) following treatment for CS and identify potential predictors for weight loss.

Methods:

A retrospective study using the Clalit Health Services database analyzed a cohort of CS patients and age-, sex-, BMI-matched controls (1:5 ratio). Weight and BMI were assessed at baseline, one year post-diagnosis, and at the end of follow-up.

Results:

The study cohort included 345 patients (63.6% women, mean age 54.2±16.40 years). One year after diagnosis (n=280), remission patients (n=160) exhibited significant weight (84.60±21.41 to 81.21±20.93 kg) and BMI (31.32±7.38 to 29.76±6.97 kg/m2) reductions (p0.01). Among 174 patients who attained remission by the end of 8.6 years of follow-up, patients (n=174) experienced BMI (30.81±7.58 to 28.86±7.64 kg/m2) and weight (82.87±21.53 to 78.62±24.92 kg) decreases (p0.01), with 47.7% achieving ≥5% and 33.3% achieving ≥10% weight loss. Patients who did not achieve remission at the end-of-follow-up showed no BMI or weight changes. Multivariate analysis identified predictors for ≥5% weight loss including female gender, baseline BMI ≥30, BMI decrease of ≥1 kg/m2 at 1 year, and dyslipidemia.

Conclusion:

Approximately half of CS patients a who attained disease remission achieved at least a 5% decrease in BMI with long-term follow-up. Disease remission, female gender, baseline BMI ≥30, BMI decrease of ≥1 kg/m2 at 1 year, and the presence of dyslipidemia predict a clinically significant weight loss.

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Denosumab is associated with decreased mortality compared to Zoledronic Acid in diabetic osteoporotic patients: a population-based cohort study.

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[3]*Medical school, Sackler Faculty of Medicine, Tel Aviv University, Israel*

[4]*KI Research Institute, Israel*

Background:

Anti-resorptive therapies are the mainstay of osteoporosis management, but evidence of their efficacy in the diabetic population is limited and comparison between treatments is lacking. A retrospective analysis, presented at the American Society for Bone and Mineral Research (ASBMR) 2023 Annual Meeting, suggests that denosumab leads to greater reduction in fracture risk than zoledronic acid among treatment-naive postmenopausal women with osteoporosis. However, a comparative study recently published suggests higher mortality with denosumab versus oral bisphosphonates.

Aim:

To assess the association between zoledronic acid or denosumab and the risk of major osteoporotic fracture and mortality in osteoporotic patients with diabetes type 2.

Methods:

The study population was identified by electronic records of a diabetes registry cross-linked with an osteoporosis registry of a large provider healthcare organization in Israel. Index date was at osteoporosis registry entry. Demographics, Charlson Comorbidity Index (CCI), diabetes complications, bone mineral density (BMD) T-scores, hemoglobin A1c levels, eGFR, purchase of statins, and anti-resorptive agents were collected. Propensity score matching was performed. Kaplan-Meier curves were generated to assess the time to outcomes. Multivariable Cox`s proportional hazards survival model was performed.

Results:

A total of 27503 diabetic osteoporotic patients were identified, 13343 (48%) patients initiated treatment; 12214 (91.5%) started an oral bisphosphonate, 627 (4.7%) zoledronic acid and 502 (3.7%) denosumab. The median follow-up was 8.9 years. The denosumab treated patients were older (75.7 vs 71.9, p0.01), had longer diabetes duration (8.4 vs 7.2, p0.01), were more frequently treated with insulin (29.7 vs 23.9, p=0.02) and had a lower eGFR (59.4 vs 75.3, p0.01). Male/Female ratio, BMI, CCI, smoking status, alcohol consumption, Hip BMD, HbA1c levels, microvascular complications, hypoglycemic events and statins prescriptions were similar. After propensity weighting, we observed a significant reduced risk of death among the denosumab treated patients (RR=0.72 [0.58-0.91]) without a significant difference in the risk of fracture (RR=0.9 [0.82-1.12]).

Conclusions:

In this cohort of diabetic osteoporotic patients, denosumab was associated with a significantly reduced mortality compared to zoledronic acid, without a significant difference in the risk of fractures. The effect of denosumab on mortality is yet to be explored.

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Impact of blood glucose control on clinical outcomes in type 2 diabetes patients hospitalized with COVID-19 infection.

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[2]*Faculty of medicine, Technion-Israel Institute of Technology, Haifa, Israel*
[3]*Statistics, Emek Medical Center, Afula, Israel*

Insufficient glycemic control in the outpatient setting is related to increased morbidity. COVID-19 infection is associated with worse outcomes in patients with hyperglycemia whether they were previously diagnosed with type 2 diabetes mellitus or not. A few studies investigated the interconnection between diabetes treatment in the community setting and diabetes treatment regimens in these patients during hospitalization for COVID-19 infection. Our study evaluates the relationship between diabetes control before and during hospitalization, the severity of SARS-CoV-2 infection, and mortality in patients with type 2 diabetes admitted with COVID-19.

Methods:

The patients were divided into four groups according to blood glucose control during hospitalization. The first group included patients with an average blood glucose ≤ 140 mg/dl, the second group included patients with an average blood glucose level between 140-180 mg/dl, the third group included patients whose blood glucose level was between 180-250 mg/dl, and the fourth group included patients with average blood glucose 250 mg/dl. In all subjects, we assessed preadmission diabetes treatment and prior diagnoses of major comorbidities (atherosclerotic cardiovascular disease, congestive heart failure, chronic renal disease, chronic pulmonary diseases, and dementia)

Glucose control during hospitalization, diabetes medications before and during hospitalization, renal function, and glucocorticoid treatment were retrieved from electronic health data.

COVID-19 death at 30 days was assessed in the four groups.

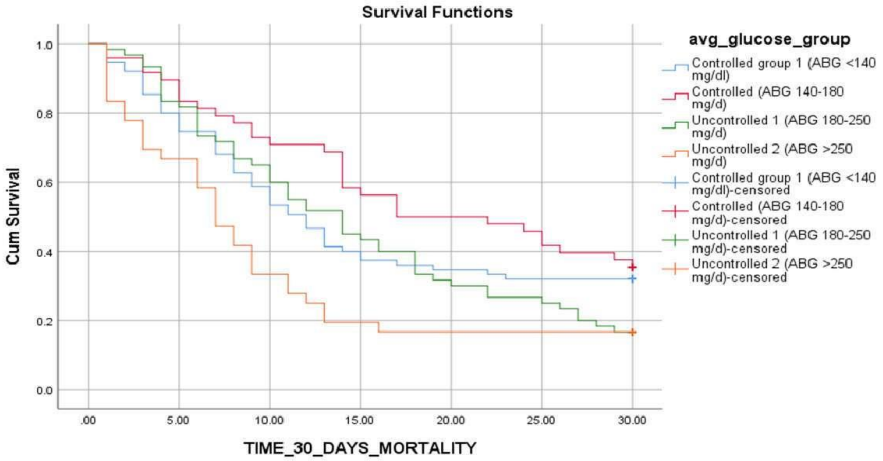
Results:

Our study found that among patients with poor preadmission glucose control (Hba1c9%), one-third had average blood glucose 250 mg/dl during hospitalization and only 8% had adequate blood glucose control. Lower preadmission Hba1c levels, insulin treatment in the hospital, and absence of acute renal failure were significant predictors of good glycemic control during hospitalization.

The overall 30-day mortality rate was 19% (192 patients out of 857) and was highest among patients with uncontrolled blood glucose during hospitalization compared to well-controlled blood glucose (32% vs. 14%). Significant predictors of mortality were the severity of COVID-19 (OR 62, CI 95%; 18-235, p0.000), acute renal failure (OR 3.2, CI 95% - 1.26-8.2; p=0.015), and a diagnosis of congestive heart failure before hospitalization (OR 2.6; CI 95% 1.14-6.8; p=0.024). After discharge, diabetes control improved only in patients with good glucose control during hospitalization.

Conclusion:

In patients with type 2 diabetes hospitalized with COVID-19, poor long-term glycemic control is associated with the level of hyperglycemia during hospitalization, and the COVID-19 severity. Patients with poorly controlled blood glucose during hospital stay had no improvement in diabetes control after hospitalization.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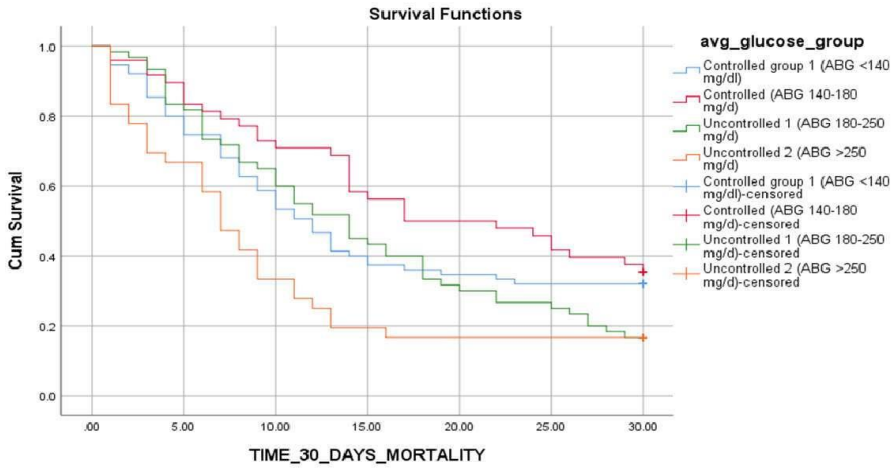
Controlled (ABG 140-180 mg/d)
Uncontrolled 1 (ABG 180-250 mg/d)
Uncontrolled 2 (ABG >250 mg/d)
Controlled group 1 (ABG <140 mg/dl)-censored
Controlled (ABG 140-180 mg/d)-censored
Uncontrolled 1 (ABG 180-250 mg/d)-censored
Uncontrolled 2 (ABG >250 mg/d)-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
5.00
10.00
15.00
20.00
25.00
30.00
TIME_30_DAYS_MORTALITY


Survival Functions
avg_glucose_group
Controlled group 1 (ABG <140 mg/dl)
Controlled (ABG 140-180 mg/d)
Uncontrolled 1 (ABG 180-250 mg/d)
Uncontrolled 2 (ABG >250 mg/d)
Controlled group 1 (ABG <140 mg/dl)-censored
Controlled (ABG 140-180 mg/d)-censored
Uncontrolled 1 (ABG 180-250 mg/d)-censored
Uncontrolled 2 (ABG >250 mg/d)-censored
Cum Survival
1.0
0.8
0.6
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0.2
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.00
5.00
10.00
15.00
20.00
25.00
30.00
TIME_30_DAYS_MORTALITY

Table 4. Logistic regression of variables predicted 30 days mortality.

Predictor variables	*Adjusted OR*	*95% CI*	*P-value*
Gender	1	0.4-2.2	0.99
Age	1.35	0.8-2.2	0.2
BMI <30	0.97	0.47- 2	0.9
HbA1C before admission	0.8	0.6-1.1	0.15
Length of Hospital stay	0.97	0.9-1.1	0.1
COVID-19 severity	12.4	6.53-25.7	<0.001
Insulin treatment	1.8	0.69-4.9	0.22
Dexamethasone treatment	0.79	0.28-2.18	0.64
Metformin treatment	1	0.34-3	0.94
SGLT-2	0.48	0.12-1.7	0.27
CRP level	1.05	1.0-1.08	0.047
Average glucose in hospital	1	0.99-1	0.74
Acute renal failure	3.85	1.52-10	0.005
Cardiovascular disease	0.57	0.28-1.9	0.13
Congestive heart failure	2.4	1.04-5.8	0.04
Chronic pulmonary disease	0.8	0.37-1.8	0.64
Chronic renal diseases	1.5	0.64-3.7	0.33

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Impact of maternal overt hypothyroidism on pregnancy complications: A nationwide cross-sectional study

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Background:

Overt hypothyroidism during pregnancy has been associated with adverse outcomes, including preterm birth, low birth weight, and impaired fetal neurocognitive development. This nationwide cohort study aimed to assess the association of elevated thyroid-stimulating hormone (TSH) levels on pregnancy complications in women with overt hypothyroidism.

Methods:

Utilizing electronic medical records from Clalit Health Services, Israel`s largest healthcare maintenance organization, data from 259,897 deliveries (2013-2022) were analyzed. The study population included all women members of CHS aged ≥18 years with available TSH results during pregnancy and who remained members throughout the gestation period. Overt hypothyroidism was defined by a mean TSH during pregnancy of ≥10. The euthyroid reference group consisted of women with maximal TSH levels 4, no documentation of prior hypothyroidism diagnosis, and without levothyroxine use.

We matched each overt hypothyroidism delivery case with 15 controls by propensity score-based matching method. Covariates considered for matching included maternal age, ethnicity, socioeconomic status, IVF in the current pregnancy, history of recurrent pregnancy loss, and smoking status.

Descriptive statistics were presented for the demographic and clinical characteristics of both groups. Univariate analysis results were reported for numeric and categorical variables. A quasi-Poisson regression model was employed to assess the risk for complications in overt hypothyroidism compared to matched controls. Incidence rate ratios (IRRs) with 95% confidence intervals were reported, adjusting to age.

Results:

The final analysis included 8,970 euthyroid and 598 overt hypothyroid pregnancies. Baseline characteristics were similar between groups. Overt hypothyroidism was charaterized by higher mean TSH levels and increased levothyroxine usage. However, there were no significant differences in gestational week of delivery or rates of preterm birth, preeclampsia, gestational diabetes mellitus, cesarean section, or intrauterine growth restriction between the groups.

The quasi-Poisson regression model did not demonstrate an increased rate of complications in the overt hypothyroidism group compared to controls. Sensitivity analyses on a parallel cohort defined by maximum TSH levels during pregnancy showed a slightly elevated risk for pregnancy complications (IRR 1.1).

Conclusion:

Our study suggests that overt hypothyroidism may not be associated with an increased risk of adverse pregnancy outcomes when adjusted for confounding factors. Our findings contribute to the ongoing discussion on the relationship between TSH levels and pregnancy complications, highlighting the importance of considering various risk factors in the analysis. Further research is warranted to explore specific diagnoses and potential nuances in this complex relationship and treatment strategies.

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Visual morbidity in macroprolactinoma: a retrospective cohort study

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Objective:

To study the visual morbidity associated with macroprolactinoma and its outcomes following medical and surgical treatment, and to identify predictors of visual recovery.

Design:

A single center retrospective cohort study.

Methods:

We reviewed patient's data including clinical presentation, serial pituitary MRI, laboratory tests, visual symptoms and neuro-ophthalmologic examination, visual field tests, and optical coherence tomography tests. The main outcome was complete visual field recovery at the end of follow-up. Patient's baseline characteristics were investigated as predictors of visual recovery.

Results:

The study cohort included 150 macroprolactinoma patients. Visual field defects at baseline were evident in 37 out of 121 men (30.6%) and 3 out 29 women (10.3%, p0.01). Patients were followed for a median of 6.0 years (IQR, 2.9-10.6).

Ten patients suffered from pituitary apoplexy (6 at presentation and 4 during follow-up), of whom 9 patients suffered from apoplexy-induced visual morbidity. Twenty-one patients had optic chiasm herniation into empty sella, of whom only 3 patients suffered from associated visual morbidity. At the end of follow-up, 24 out of 39 available visual field tests (61.5%) exhibited complete visual field recovery. Patients that achieved complete visual recovery had smaller macroadenomas [median (IQR), 30.5 mm (15.0-80.0) vs 42.0 mm (30.0-85.0), p0.01], lower serum prolactin levels [1414 ng/ml (489-3586) vs 4119 ng/ml (2715-6315), p0.01], lower rates of central hypogonadism (78.3% vs 93.3%, p=0.05) and central hypothyroidism (20.8% vs 53.3%, p=0.04), lower rates of compressive optic neuropathy (35.3% vs 87.5%, p=0.02), and a better visual acuity (better than 6/8 in both eyes, 93.7% vs 28.6%, p0.01).

In patients who required optic tract decompression at diagnosis (n=25), we found no differences in visual recovery rates between surgically-treated (5 out of 11, 45.5%) and medically-treated (8 out of 14, 57.1%) patients (p=0.56).

Conclusions:

In our cohort of 150 macroprolactinoma patients, 26.7% of patients presented with visual field defects at baseline, with higher rates of visual field damage among men.

Patients that achieved complete visual recovery had smaller macroadenomas, lower serum prolactin levels, lower rates of central hypogonadism and central hypothyroidism, lower rates of compressive optic neuropathy, and a better baseline visual acuity.

Given the limited sample size, we found no differences in visual recovery rates between surgically-treated and medically-treated patients who required optic tract decompression.

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Unraveling the Metabolic and Endurance Effects of Novel PPAR-δ Agonists in Mice: Implications for Therapeutic Strategies in Metabolic Disorders.

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Introduction:

Peroxisome proliferator-activated receptors (PPARs) are key nuclear receptor proteins that govern diverse physiological processes. Among the PPAR subtypes, PPAR-δ has emerged as a crucial regulator of energy metabolism, inflammation, and cellular differentiation. In this study, we explored the impact of novel PPAR-δ agonists, GNF_0242 and GNF_8065, in comparison with the established agonist GW501516, on physical endurance and metabolism in mice.

Methods:

We employed both in vivo and in vitro models, with potential therapeutic implications for metabolic health and endurance performance. In the in vivo model, mice undergoing moderate treadmill running were treated with PPAR-δ agonists for 21 days. Endurance and metabolic parameters were assessed through exercise stress tests and metabolic analyses, respectively. In the in vitro model, cultured myoblasts differentiated into multinucleated myotubes and treated with PPAR_ δ agonists, RT-PCR wase used to quantify the expression levels of mitochondrial genes.

Results:

Our findings revealed that PPAR-δ agonist treatment significantly increased running endurance, enhanced fatty acid utilization, and elevated total energy expenditure, while concurrently reducing respiratory quotient, serum triglyceride levels, and body fat percentage. Notably, the GNF_8065-treated group exhibited enhanced cumulative food and water intake, particularly during the dark phase, indicating a unique metabolic response. Fatty acid oxidation was significantly elevated in groups treated with GNF_0242 and GNF_8065 compared to GW501516 and control groups. Moreover, a noteworthy reduction in carbohydrate oxidation during the light phase was observed in the GNF_8065 group. In the in vitro model, myoblasts isolated from skeletal muscle tissue exhibited upregulated genes associated with mitochondrial fatty acid metabolism upon treatment with PPAR-δ agonists.

Conclusions:

Our findings align with PPAR-δ`s established role as a regulator of lipid metabolism, emphasizing its potential to enhance muscle fatty acid oxidation and total energy expenditure. This sheds light on the mechanisms through which PPAR-δ activation influences energy substrate utilization in muscle cells. In essence, our research provides valuable insights into the metabolic and endurance effects of novel PPAR-δ agonists, paving the way for targeted therapeutic approaches in metabolic disorders, cardiovascular diseases, and inflammatory conditions. The comprehension of the intricate functions and mechanisms of PPAR-δ holds significant promise for advancing human health and performance.

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Nonsurgical management of pheochromocytoma in the very elderly – a case series and review of the literature

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Introduction:

Pheochromocytoma (PCC) is a rare tumor with potentially fatal complications, namely cardiovascular events and PCC spells. Few cases of PCC treated non-surgically in the elderly have been described.

Methods:

we collected data regarding three PCC patients that did not undergo adrenalectomy for various reasons on an average follow up of 5.61 years.

Results:

patient 1 was 75 years old (YO) at diagnosis, he had a tumor diameter of 3.2 cm and refused surgery. He had a stroke 6.6 years after diagnosis and remained alive on a follow up of 9.25 years. His first available 24-hour urinary metanephrines and normetanephrines were 5.91 and 1.98 times upper normal limit (UNL) respectively. On 2.34 years follow up, 24-hour urinary metanephrines and normetanephrines were lower: 3.88 and 1.85 times above UNL respectively. Blood pressure (BP) treatment was with ramipril and doxazosin.

Patient 2 was 86 YO when he had an adrenal mass of 4.9*6.2*4.5 cm found on CT, he wasn`t referred to workup at that time and workup was complete only 7.31 years later, at age 94 YO when the adrenal mass was 7.4*8.1*8.8 cm and 24-hour urinary metanephrines, normetanephrines and methoxytyramine were 12.73, 15.51 and 1.42 times the UNL respectively. His BP and heart rate (HR) were controlled with doxazosin and metoprolol, he had no cardiovascular events during this time.

Patient 3 was 85 YO at diagnosis, with tumor dimensions of 4.5*5.5, she had a positive F-DOPA scan, refused urinary metanephrines collection or any other workup, on a follow up of 0.28 years her BP and HR were controlled with doxazosin, lercanidipine and bisoprolol, she remained alive and had no cardiovascular events.

Our average age at diagnosis was 82 years, and average follow up time was 5.61 years. during follow up there was no mortality, one case of stroke, no other cardiovascular events were recorded. One patient had been hospitalized due to a syncope 2.40 years after diagnosis and another was hospitalized due to urological problems. Average age at end of follow up was 88 years.

Conclusion:

in this series of three elderly patients with PCC that did not have an adrenalectomy we found one occurrence of a stroke and no other cardiovascular events or death of any cause on a follow up of 5.61 years. It thus seems that medical management may allow satisfactory disease control in select cases in which surgery is not possible or refused by very elderly patients.

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Research Portal for Single-Cell RNA Atlas of Human Pancreatic Islets

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Pancreatic endocrine islets comprise alpha, beta, delta, pp.gamma, and epsilon cells, each with distinct functions in glucose homeostasis. Dysfunction of these cells is the hallmark of type 1 and type 2 diabetes (T1D, T2D). Single-cell RNAseq studies have provided valuable insights into the biology of these cells. While the data of these studies is publicly available, extracting the biological information remains difficult due to the complexity and large number of technical parameters involved in quality control, integration and visualization of single-cell RNAseq data.

In this study, I offer integrated RNA sequencing data of 76,267 curated human endocrine pancreas cells collected from 66 donors (39 healthy donors,17 were diagnosed with T2D and 10 were diagnosed with T1D), all sourced from the Human Pancreas Analysis Program (HPAP) , the most extensive public dataset. We performed rigorous quality control, extracted the endocrine cells, and constructed a research portal designed for diabetes researchers, providing multiple options for gene expression visualization. https://singlecellrnapancreas.shinyapps.io/DBen/

We utilized the data to investigate the effects of aging on the alpha, beta and delta cell transcriptome and found that oxidative phosphorylation pathway is downregulated in the alpha, beta and delta cells of older females, and upregulated in alpha and beta cells of older males. We also observed an association between aging and a decline in the expression of genes related to estrogen signaling and testosterone metabolism.

Focusing on T2D, genes correlated with HbA1C (Hemoglobin A1C) levels were enriched in DNA repair pathways. Genes correlated with ALDOB, a gene overexpressed in T2D, were enriched in the TNF-α signaling via NFκB pathway reinforcing the role of inflammation in T2D.

Altogether, we generated a well curated high-quality single cell RNAseq data from a publicly available source and made it available for researchers without any bioinformatic skills. We used this data to identify associations between age and type 2 diabetes, and changes in metabolic and hormonal pathways.

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Hyperinsulinemia and the insulin secretion threshold

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The main function of pancreatic β-cells is to produce insulin, sense glucose, and secrete insulin when extracellular glucose levels rise over a set-point. When the plasma glucose concentration increases, glucose enters the β-cells and is metabolized to generate ATP. A rise in the ATP/ADP ratio closes ATP-sensitive K channels, initiating insulin secretion. However, not all the glucose is used by β-cells to generate ATP. Cataplerotic reactions use TCA intermediates to generate amino acids, which are then used in other processes, such as insulin biosynthesis. In consequence, not all of the glucose that enters the cell is translated to ATP. Indeed, published data and our preliminary findings show that 13C labeled glucose is metabolized into amino acids when given to human and mouse islets in vitro.

We hypothesize that hyperinsulinemia, which is characterized by increased secretion and therefore biosynthesis of insulin in β-cells, will increase the metabolic flux through cataplerotic reactions, leading to a reduction in ATP generation from glucose, and incorrect sensing of extracellular glucose levels.

In support of this hypothesis, analysis of human single-cell RNAseq data shows that β-cells of type 2 diabetes patients are characterized by differential expression of cataplerotic enzymes and amino acid transporters. Mathematical modeling using flux balance analysis shows that an increase in insulin biosynthesis increases the flux of cataplerotic reactions in the cell, resulting in a reduction of ATP generation from glucose. We modeled hyperinsulinemia in vitro by treating mouse islets with sulfonylurea, and detected a shift in the insulin secretion curve in hyperinsulinemic islets. We plan to use this model for Calcium imaging and to measure ATP synthesis and incorporation of glucose into insulin in normo- and hyperinsulinemic conditions.

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Is parity a risk factor for differentiated thyroid carcinoma? A population-based case-control study

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Background:

Female gender is an established risk factor for differentiated thyroid carcinoma (DTC). A potential explanation is that reproductive factors increase the risk of thyroid tumorigenesis.

Aim:

Soroka University Medical Center provides health services for a population characterized by many live births every year, many of which are delivered by grand multiparous women. Herein, we aimed to evaluate the association between parity and the risk of DTC in this unique population.

Methods:

This was a population-based case-control study. Female patients diagnosed with DTC between 01/1982 to 12/2022 comprised the 'cases' group. The 'control' group was created by retrieving data from the same databases and consisted of three female individuals per each 'case', matched by year-of-birth and by ethnicity. Main exclusion criteria were prior malignancy (other than DTC) or prior radioactive iodine treatment for non-malignant thyroid disease. Primary exposure was defined as the number of deliveries before the diagnosis of DTC. Relevant demographic, clinical, and obstetric data were retrieved from the individual electronical medical records and were compared between groups using descriptive statistics. Multivariable analysis, adjusted for socioeconomic status, TSH levels, oral contraceptive use, rates of autoimmune thyroid diseases, and BMI, was used to assess the association between parity and DTC risk.

Results:

Following rigorous screening process, 300 'cases' and 900 'controls' were included. Generally, baseline characteristics were comparable between groups: median age at diagnosis was 39 years (range 21-65) and 26 years at first delivery; Mean TSH±SD was 2.4mIU/L±2.9 ('cases') versus 2.2mIU/L ±1.6 ('controls'), p=0.427; BMI was ~27 in both groups. As opposed, the rates of Hashimoto thyroiditis (9.7% versus 1.8%, p 0.001), and Graves' disease (6.3% versus 2.7%, p = 0.005) were higher among 'cases'. The median number of deliveries was 3 (range 0-15) in both groups. However, multivariable analysis revealed that when compared to women with 1-5 deliveries, there was a significant association between DTC risk and both, six deliveries or more (OR=1.829, 95% CI: 1.303–2.569) and nulliparity (OR=1.762, 95% CI: 1.185–2.622).

Conclusion:

Our study, which included high proportion of grand multiparous women, displayed a positive association between the presence of autoimmune thyroid diseases and DTC risk. Moreover, we demonstrated a positive association between nulliparous and women with 6 deliveries or more and DTC risk as compared with women who experienced 1-5 deliveries. Further research is warranted to elucidate underlying mechanisms and validate these findings across diverse populations.

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Exploring a rare association: pathophysiology and treatment of hypercalcemia in non-tuberculosis mycobacterium infections

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Hypercalcemia is a rare complication of non-tuberculous mycobacterium infections, particularly in the context of human immunodeficiency virus positivity. This study presents a systematic review of non-tuberculous mycobacterium (NTM) associated hypercalcemia, including a unique case of Mycobacterium simiae-induced hypercalcemia in an HIV-infected patient. A comprehensive literature search identified 24 relevant cases (11 HIV-positive, 13 non-HIV) included in the analysis. The clinical and laboratory characteristics of these cases revealed distinct profiles between HIV and non-HIV patients. Patients in the HIV group, despite having severe immunodeficiency, developed hypercalcemia typically after highly active antiretroviral therapy initiation or NTM infections treatment. In non-HIV patients, various underlying immunosuppressive conditions, such as chronic renal failure and immunosuppressive drug use, were associated with NTM-induced hypercalcemia. The pathophysiology of NTM infection-induced hypercalcemia is possibly caused by two distinct mechanisms: immune restoration leading to granuloma formation and 1,25-dihydroxyvitamin D production, or prolonged immune suppression allowing for NTM infections-related macrophage activation. Treatment strategies, including bisphosphonates, steroids, and hemodialysis, were employed, with bisphosphonates emerging as effective and safe.

This study emphasizes the need for heightened clinical awareness regarding non-tuberculous-mycobacterium-induced hypercalcemia, particularly in immunocompromised patients. It also highlights the importance of understanding the timing of immune response restoration in the context of NTM-infection therapy initiation. Further research is warranted to explore predictive factors for treatment response and in order to refine therapeutic guidelines in NTM-associated hypercalcemia.

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Prolonged Fasting Test - One tertiary center experience

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Introduction:

The prolonged fasting test (PFT) is a widely accepted method for evaluating hypoglycemia of unknown origin. In most cases, secondary causes unrelated to endogenous insulin excess are identified. These causes include bariatric surgeries, IGF2 secretion, and misdiagnosis of true hypoglycemia. Limited data regarding the yield of PFT for hypoglycemia assessment currently exists.

Methods:

Our study reviewed all fasting tests conducted at Hadassah Ein Kerem Medical Center between the years 2010 and 2020. Patient identification was performed using insulin and C-peptide tests taken at the hospital. Patient records were reviewed to identify those who underwent PFT. Patients under 16 and those evaluated during psychiatric hospitalization were excluded.

Results:

The study included 64 patients, with ages ranging from 16 to 83 (average 43.9); 55% were female. Sixteen patients (25%) had undergone a PFT before the current examination, with 13 having done a short fasting test and 3 having a full 72-hour fasting test. Whipple`s triad was observed in 28% of the participants, and 57% had hypoglycemia documented by the medical staff before the PFT. Sixteen percent had undergone bariatric surgery. PFTs were performed as an elective procedure in 63% of patients, with an average duration of 50 hours. Forty-three percent of the tests were completed after a total of 72 hours. The reasons for test termination were planned completion time, hypoglycemia with symptoms, and asymptomatic hypoglycemia in 50%, 36%, and 11% of tests, respectively. Sixteen (25%) PFTs supported the diagnosis of endogenous insulin secretion, while 4 PFTs yielded ambiguous results.

A final diagnosis was documented in 25 patients. Documented final diagnoses based on fasting tests include insulinoma (15), bariatric surgery-related hypoglycemia(3), reactive hypoglycemia (1), alcohol-related hypoglycemia((1), exogenous insulin(2), IGF-2 secretion (1), and congenital multi-system syndrome(1).

Discussion:

PFT is the ultimate test for identifying endogenous hyperinsulinemia. However, it requires hospitalization and can last up to 72 hours, causing significant discomfort to patients and burdening the hospital medical team. Our data shows that some patients are referred to PFT without clear evidence of Whipple`s triad, and sometimes even in the presence of previous bariatric surgery, suggesting alternative etiologies for hypoglycemia. Most PFTs lack evidence of using glucagon or exercise after completing the test. Unfortunately, a significant proportion of fasting tests conclude without demonstrating hypoglycemia.

Conclusion:

The results emphasize the need for cautious use of the fasting test. However, an efficient alternative to this test has not been found.

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Analysis of type 1 diabetes trends in Israel

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Background and Aims:

With increased awareness of late-onset type 1 diabetes and the importance of accurate diabetes classification, there is a need to reassess the epidemiological and clinical characteristics of pe

ople with T1D (PwT1D). We report analyses of a novel population-based cohort of PwT1D in Israel.

Methods:

Using database of Clalit HMO in Israel, insuring 4.8M people (51.5% of the population) we established a registry of all PwT1D. Prevalence, annual incidence, assessment of anthropometric, metabolic parameters, diabetes-related complications, and comorbidities were analyzed.

Results:

We recorded data of 13,167 PwT1D (0.27% of the population, 51.3% men), with an annual incidence of 1.05/10,000 people representing a 13% increase over the past decade. Median age at diagnosis is 22 years with 25% diagnosed at age ≥40 years. Median age of current PwT1D is 36 years with 25% are ≥55 years of age. Of note, 50% are either overweight or obese, with over 50% having metabolic abnormalities, traditionally associated with type 2 diabetes. Hypothyroidism (16.1%) and Celiac disease (4.5%) are the most prevalent autoimmune diseases in this cohort. Additional characteristics are depicted in table 1.

Conclusion:

Currently, a significant proportion of PwT1D are of middle age or older, about half are overweight or obese with the majority having additional characteristics of the metabolic syndrome. Efforts for accurate classification of PwT1D and addressing associated comorbidities are of key importance.

Table 1: characteristics of PwT1D

Current Age	
Mean (SD)	39.4 (21.1)
Median, 25-75 IQ	36 [22; 55]
Age at diagnosis	26.6 (18.1)
Mean (SD)	22 [12; 39]
Median, 25-75 IQ	
Sex	
Women	48.7 %
Men	51.3 %
Use of advanced technologies (N; %)	
Continuous glucose monitoring	5,265 (39.6%)
Continuous subcutaneous insulin infusion	7,656 (57.6%)
BMI (Kg/m²)	
Before diagnosis	23.2 (31.7)
Current	26.1 (8.5)
% Overweight	29.3%
% Obesity	19.6%
	5.0%
Smoking status (%)	30.2%
Past	
Current	
Co-morbidities (N; %)	
Metabolic:	
Hyperlipidemia	7,839 (58.9%)
Hypertension	4,171 (31.4%)
Ischemic heart disease	2,277 (17.1%)
Stroke	1,112 (8.4%)
Diabetes-related complications (N; %)	
Retinopathy	3,239 (24.4%)
Diabetes Kidney Disease	
- CKD	1,422 (10.7)
- Dialysis	359 (2.7%)
- Renal transplantation	196 (1.5%)
Lower limb amputation	461 (3.1%)
Autoimmune diseases (N; %)	
Hypothyroidism	2,144 (16.1%)
Celiac Disease	601 (4.5%)
Hyperthyroidism	330 (2.5%)
Addison's Disease	39 (0.3%)

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Impact of anti-osteoporosis medications on the risk of recurrent hip fracture

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Background:

Osteoporotic hip fractures (OHF) are associated with morbidity, mortality and high risk of a second hip fracture.

Objective:

To evaluate incidence of second OHF and determine the effect of anti-osteoporosis medication on this risk.

Methods:

This retrospective population-based study included all patients 50 years and older, insured by Clalit Health Services (CHS) nationwide, who were operated for OHF at any of CHS hospitals between January 2012 and December 2021. Inclusion criteria were hospitalization with the diagnosis of OHF and surgical repair of the fracture using ICD-9 codes. Main exclusion criteria were malignancy diagnosed in the 3 years prior to the first fracture, periprosthetic, and sub-trochanteric fractures. MDClone platform was used to retrieve demographic, clinical, biochemical, and drug purchase data from CHS electronic records. Hazard ratios for second OHF were assessed by using univariable and multivariable Fine & Grey regression models, that account for the competing risk of death.

Results:

Among the 9425 patients with OHF who met our study criteria, 645 (6.8%) experienced a second OHF, 5140 patients (54.5%) died without a second hip fracture, and 3640 (38.7%) were alive without a second OHF at end of follow-up. Median follow-up was 3.4 years (IQR:1.7, 5.7). The median time to a second OHF was 2.1 years (IQR:0.7, 4). The average age at first fracture for patients with a second fracture was comparable to that of the entire study population (80±9 vs. 80±10 years, respectively).

After their initial fracture, 17% of patients who later experienced a second OHF received oral bisphosphonates, compared to 12.7% of those who did not suffer a second fracture. Fifteen percent of the second-fracture group received Zoledronic acid and/or Denosumab compared to 20.8% of those who did not experience a second fracture.

In multivariable analysis adjusted for age, sex, Charlson Comorbidity Index and socioeconomic score at first OHF, patients who received Zoledronic acid and/or Denosumab after their initial hip fracture, and throughout the follow-up period, showed a significantly lower risk of a second OHF, compared to those without any medication (HR: 0.65 CI 0.52-0.82). Conversely, no significant difference in risk was shown for oral bisphosphonates (HR: 1.18, CI 0.95-1.46). Similar effects were observed in patients who received these medications within 2 years of their first OHF.

Conclusion:

Administration of Zoledronic acid and/or Denosumab after the first OHF was associated with a significant risk reduction in second OHF.

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Osteitis fibrosa cystica recovery following parathyroidectomy for primary hyperparathyroidism: a case series and review of literature

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Objective:

Osteitis fibrosa cystica (OFC) is an extreme manifestation of accelerated bone resorption in primary hyperparathyroidism (PHPT), rarely encountered nowadays. Bone mineral density gain following parathyroidectomy (PTx) is well documented, while little is known regarding the timeline of re-mineralization and recovery of the lytic lesions

Materials and methods:

We present three patients with clinical, biochemical, and advanced (computer tomography or magnetic resonance) imaging post-PTx follow-up and review published similar OFC patient cases reporting serial imaging of bony lesions following PTx.

Results:

The main baseline patient's characteristics are presented in table 1. All patients received calcium, magnesium, and alfacalcidol supplementation post PTx; and serum calcium, PTH and alkaline phosphatase normalized gradually. Patients 1 and 2 demonstrated an impressive re-mineralization of pelvic lytic lesions within 6 and 12 months following PTx, respectively. Patient 3 had partial re-mineralization in the C4-C5 vertebrae in 6 months, which continued to progress 18 months after PTx. We summarized reports of fifty-four patients with PHPT and OFC, assessed for lytic lesion recovery after PTx with different imaging modalities. Most lesions were partially re-mineralized within 6-12 months. Near-complete remineralization was evident in 38 (70.3%) on the last imaging follow-up.

Conclusion:

Lytic lesions of OFC undergo recovery following successful PTx; however full mineralization may take longer than a year. This timeline should be taken into account when considering the possibility of salvage orthopedic surgery. Active surveillance may be advised in most cases, excluding large lesions in weight-bearing areas, which are more prone to fracture.

Table 1- main patients' characteristics

	Patient 1	Patient 2	Patient 3
Age at diagnosis	24	41	67
Gender	Female	Male	Male
PTH, x ULN	12.7	26.3	16
Albumin corrected Calcium mg/dl	13.2	13.9	13.8
25-OH-Vitamin D, ng/ml	12.5	5.7	10
Alkaline phosphatase, x ULN	4.8	10.2	2.5
Location of lytic lesions	Mandible, ilium, ischium, femoral shaft	Ilium, ischium, vertebras	Cervical vertebra, ilium, femoral neck and trochanter
Salvage orthopedic intervention	Intramedullary nailing of left femur (after PTx)	None	Corpectomy of level C4-C6 and excision of the extramedullary lesion (Before PTx)

Key: PTH- parathyroid hormone; PTx- parathyroidectomy; ULN- upper limit of normal

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The incidence of fractures in cancer patients initiating immune check-point inhibitors

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Introduction:

Immune check-point inhibitors (ICI) can cause adverse events in many organs due to the activation of T-cells. Data on the effect of ICI on bones and incidence of fracture is still scarce.

Aim:

To quantify the rate of osteoporotic fracture before and after the use of ICI in cancer patients.

Methods:

We retrospectively retrieved pertinent data of all patients who were treated with ICI between 2015 and 2023 at the Tel-Aviv Souraski Medical Center. Healthcare administrative databases were assessed for the presence of fracture diagnostic codes in the year prior to and up to two years after ICI initiation. Fracture rate was stratified based on the time-period before and after ICI initiation.

Results:

The study cohort consisted of 1349 ICI users. The mean age was 67.7 (10.9) years, 58% were male, 35.5% were active smokers, 18% were diabetics, mean BMI was 25.7 (6.8) and mean Charlson Comorbidity Index was 4.2 (2.3). Most patients were treated with an anti-PD-1 agent (82.1%), for 17.6% it was the only therapy. The fracture rate in the year prior to ICI initiation was 8.9 per 1000 patient-years. The fracture rate in the year after ICI initiation was 12 per 1000 patient-years. The fracture rate in the second year after ICI initiation was 18.9 per 1000 patient-years. In the first and second years after ICI treatment initiation, incidence rates of fractures were higher compared to the last year prior ICI treatment, IRR=1.34 (95% 0.64-2.85) and IRR=2.13 (95% 1.02-4.41), respectively. Only 12.5% of the patients who sustained a fracture received an antiresorptive treatment.

Conclusions:

Fracture risk may be increased in cancer patients after initiation of ICI. Prospective studies monitoring BMD in addition to fracture rate are needed. An effort should be made to identify patients at risk for fractures and offer adequate therapy.

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Senolytics Dasatinib and Quercetin alleviate TypeI Diabetes-related cardiac fibrosis in AKITA mice

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Only a few studies have examined the underlying mechanisms of heart failure in type 1 diabetic (T1D) patients. Diabetes-induced hyperglycemia is implicated in the development of diabetic heart responses such as cardiomyocyte hypertrophy, fibrosis, and oxidative stress, termed diabetic cardiomyopathy. As a severe complication of diabetes, diabetic cardiomyopathy is associated with structural and functional changes of the heart leading to left ventricle hypertrophy as well as diastolic and systolic dysfunction that can develop independently of hypertension and coronary artery disease. Myocardial fibrosis and collagen deposition are structural changes observed in diabetic cardiomyopathy. Collagen type I and III are major structural proteins of the myocardial extracellular matrix which provide architectural support for the muscle cells and play an important role in myocardial function. The differential expression of Collagen I and III as well as the difference in the Collagen I/Collagen III ratio are important in different types of heart diseases. This importance arises from the differences in their mechanical properties where Collagen I increases the strength and stiffness while Collagen III increases elasticity of the tissues. The therapeutic strategies available to date for T1D-related cardiomyopathy focus on controlling hypertension, renal function, blood glucose and lipids. There are no effective drugs targeting myocardial fibrosis. In this study we explored the effect of senolytics Dasatinib (D) and Quercetin (Q) on Collagen I and III expression in AKITA$^{Ins-/+}$ mice, a model for T1D. Three months AKITA$^{Ins-/+}$male and female mice were randomly assigned to treatment with either Dasatinib (5 mg/kg) and Quercetin (50 mg/kg) or control vehicle administered once monthly by oral gavage for a total of four months. Left ventricle heart lysates were prepared for the determination of relative mRNA expression by RT-PCR using SYBR Green and normalized to *Polr2a* expression, and Collagen 1 protein by Western Blotting. Treatment with D+Q resulted in two-fold decrease in Collagen1 (0.768±0.117 vs. 0.3477±0.082, p=0.011) and 1.6-fold increase in Collagen 3 (0.9322±0.0945 vs. 1.475±0.164, p=0.011) RNA expressions with a two-fold decrease in the Collagen I/ Collagen III ratio (0.877±0.096 vs. 0.384±0.1, p=0.0093) in male mice. In females, relative mRNA expression was not different in treated vs. untreated mice. Western blotting analysis showed a 2.0-fold decrease in protein levels of collagen 1 in treated versus untreated AKITA$^{Ins-/+}$ male mice (1.127±0.221 vs. 0.578±0.143, p=0.042). Our results represent a first report of the therapeutic potential of senolytics (D+Q) to reduced myocardial fibrosis in T1D-related cardiomyopathy.

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Inhibition of Somatostatin Secretion Promotes Complete Remission of Diabetes in Mice

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Background:

The progressive decline of beta-cells is a hallmark of all forms of diabetes, spurring extensive research into their regeneration. A promising strategy involves the endogenous regeneration of beta-cells within the patient, achievable through self-replication, transdifferentiation from other differentiated cells, or neogenesis from intrinsic progenitor cells. Our team has recently developed an advanced mathematical model that accurately simulates complex biological systems, including glucose regulation in both healthy and diabetic states. Intriguingly, this model suggests that suppressing the secretion of somatostatin (distinct from antagonizing its signaling pathways) could trigger the restoration and stabilization of insulin-producing beta-cells.

Methods:

To test this hypothesis, diabetes was experimentally induced in both wild-type and genetically modified mice lacking somatostatin through alloxan treatment. These mice were then observed over a 90-day period, with regular monitoring of their blood glucose levels. Additionally, in a separate experiment, wild-type mice with newly onset diabetes were treated with a drug delivered via osmotic pumps, which was identified to inhibit somatostatin secretion.

Results and Conclusions:

Our forthcoming presentation will unveil the empirical confirmation of our model`s predictions. We observed that mice deficient in somatostatin displayed a complete reversal of diabetes symptoms and achieved total insulin independence in the context of chemically induced diabetes. Furthermore, the identification and application of a pharmacological inhibitor of somatostatin secretion also resulted in a full recovery from diabetes, thus offering a potential new therapeutic avenue for diabetes treatment.

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Changes in emotional and uncontrolled eating induced by GLP1a associated with weight loss, weight regain and drug cessation

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Introduction:

GLP1a, by acting on stress response and emotion regulation, could have the potential to reduce emotional eating (EE) and uncontrolled eating (UE).

Methods:

A survey was sent to patients in a hospital-based weight management clinic and posted to Facebook. To assess the relationship between GLP1a and eating behaviors, respondents were asked to complete the widely used Three-Factor Eating Questionnaire Revised 18 item version (TFeRQ-18) twice by recalling the maximal effect of GLP1a vs. being off therapy. The TFeRQ-18 consists of 3 scales assessing UE, EE and cognitive restraint (CR), with higher scores indicative of more of each behavior.

Results:

Between July and August 2023, 257 responses were collected from PwO taking GLP1a over the past 2 years. Mean age was 53±13 and baseline BMI 37.7±7.0 kg/m2. Seventy percent of respondents were female and 22% endorsed T2DM. Semaglutide use was reported by 209 subjects (81%), taking 1.1±0.5mg weekly for 24±18 months, and liraglutide by 48 (19%), taking 2.5± 0.7mg daily for 17±13 months. Overall weight loss was 11.8±11.9% and 7.0±7.6% for semaglutide and liraglutide users respectively (p=0.003). Weight regain during continued drug use was 3.5±8.3% and 6.1±12.3% for semaglutide and liraglutide users respectively (p=0.09). Comparing semaglutide to liraglutide users, there were higher rates of drug cessation for the latter (29 vs. 42%, p=0.08), with side effects more often cited as the main reason for discontinuation (48.3 vs. 65.0%, p=0.052). There were improvements in eating behaviors assessed by TFeRQ-18 on therapy.

There was a positive correlation between overall weight loss and reduced UE and EE on GLP1a (r=0.31 and r=0.29, p

Conclusion:

In PwO treated with GLP1a, weight loss is associated with reduced UE and EE on treatment, while a rise in these behaviors is associated with weight regain. Less improvement in UE, EE or CR is associated with drug cessation.

Table 1: Baseline Characteristics and GLP1 Analog Use

Characteristic	All subjects (n= 257)	Semaglutide (n=209)	Liraglutide (n=48)	P Value
Age (years)	53±13	53±12.9	53±13	0.72
Female	181 (70%)	150 (72%)	31 (65%)	0.33
Weight before drug (kg)	105.3±22.6	104.8±22.5	107.2±22.6	0.53
BMI before drug (kg/m^2)	37.7±7.0	37.6±6.8	38.2±7.9	0.83
History of bariatric surgery	45 (18%)	40 (19%)	5 (10%)	0.15
Medical Comorbidities				
Dyslipidemia	84 (33%)	58(28%)	26 (54%)	0.81
HTN	79 (31%)	60 (29%)	19 (40%)	0.12
NAFLD/NASH	66 (36%)	53 (25%)	13 (27%)	0.86
T2DM	56 (22%)	54 (26%)	2 (4%)	0.001
Psychiatric disorders	37 (14%)	25(12%)	12 (25%)	0.02
GLP1 analog use				
Mean drug dose (mg)		1.1 ±0.5	2.5 ± 0.7	
¥Length of treatment (months)	18.4±16.6	[i]24±18	[ii]17±13	0.007
Respondents reporting taking drug 80-100% of time	80	60 (75%)	20 (25%)	0.33
*Overall weight loss (%)	11.3±12.4	11.8±11.9	7.0±7.6	0.003
#Maximal weight loss on drug (%)	14.1±9.3	14.9±9.3	10.8±8.6	0.17
‡Weight regain on drug (%)	4.0±9.3	3.5±8.3	6.1±12.3	0.09
*Overall weight loss (kg)	10.9±11.3	12.3±13	7.2±8.3	0.90
#Maximal weight loss on drug (kg)	14.7±10.5	15.5 ±10.7	11.2 ±8.9	0.09
‡Weight regain on drug (kg)	3.4±7.8	3.2 ±7.8	4.0± 7.5	0.62
Months to achieve nadir	10.2±8.1[i]	10.9 ±8.4[iii]	7.4 ±6.0[iv]	0.19
Δ TFeRQ-18 EE	24.1±27.8	24.7±28.4	21.5±25.5	0.262
Δ TFeRQ-18 CR	-6.7±23.4	-6.4±28.8	-8.0±21.6	0.693
Δ TFeRQ-18- UE	17.3±28.4	17.3±28.9	17.6±26.3	0.960

¥ length of treatment at time of answering survey or until drug cessation*Overall weight loss: baseline weight minus last weight on therapy #Maximal weight loss: baseline weight minus nadir weight on therapy ‡Weight regain: last weight on therapy minus nadir weight on therapy. [i]missing data (n=138) [ii]missing data (n=238) [iii]missing data (n=191) [iv]missing data (n=47). Δ TFeRQ-18- Changes in Three-Factor Eating Questionnaire Revised 18 item version EE- emotional eating, CR- cognitive restraint, UE- uncontrolled eating. Change in TFeQ-18 scores reflect values off therapy minus value on therapy during perceived maximal effect. *Overall weight loss: baseline weight minus last weight on therapy

Table 2: Correlations between weight and TFeQ-18 on GLP1a

	Δ uncontrolled eating (UE) scale	Δ emotional eating (EE) scale	Δ cognitive restraint (CR) scale
*Overall % weight loss	0.31 (<0.001)	0.29 (<0.001)	-0.09 (0.15)
‡Weight regain on drug (Kg)	-0.16 (0.01)	-0.12 (0.052)	0.01 (0.85)
Age	-0.23 (<0.001)	-0.15 (0.02)	-0.05 (0.5)
Baseline BMI	0.04 (0.52)	-0.08 (0.21)	-0.09 (0.14)

Spearman correlation used to calculate reported r-values. p-value listed in parentheses. Change in TFeQ-18 scores reflect values off therapy minus value on therapy during perceived maximal effect. *Overall weight loss: baseline weight minus last weight on therapy ‡Weight regain: last weight on therapy minus nadir weight on therapy.

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Adrenocortical Carcinoma – A Tertiary Center`s Recent ~10-year Experience.

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Background:

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with a poor prognosis. Prospective randomized controlled studies to evaluate the optimal treatment modalities are limited. Therefore, retrospective studies are needed. The aim of the study is to describe and summarize additional data and knowledge on treatment modalities in a tertiary medical center treating patients with ACC by a multidisciplinary expert team.

Methods:

A retrospective study.

Results:

The study cohort included 42 subjects (57% females), followed for a median of 26 (range 0.3-237) months. The mean age at diagnosis was 54±17 years; 60% of tumors were functioning, 57 % were cortisol-secreting, 41% were androgen-secreting, 12% aldosterone-secreting, and 45% were co-secreting. ENSAT stage at diagnosis was stage 1 in 19%, stage 2 in 26%, stage 3 in 24% and stage 4 in 29%. Eighty-eight % of patients underwent surgery; residual disease was in 21% post surgery. Treatment with mitotane was initiated in 62% of patients, reaching a mean maximal dose of 3.1 ±2 grams/day. Oncologic pharmacological treatment (Chemotherapy, TKI, Immunotherapy) and/or radiation were given in 50 % and 21%, respectively. In 14 /42 patients, genetic evaluation was done, in most cases, no target for treatment was found.

52% of patients died during follow-up; all cohort median time to death was 31(range 0.3-237) months. Time to death longer than 31 months was also seen in advanced disease stage 3- 3/9(33%) and stage 4-4/11(36%). Except association between mitotane and prolonged time to death (p=0.013), no other factors (age, gender, surgery, radiation, residual disease functional status), were associated with prolonged survival.

Conclusions:

ACC remains a rare disease with a poor prognosis. However, it is a heterogeneous disease, with some patients with advanced disease achieving more prolonged survival. Further characterization of these patients may improve our understanding of the biology and treatment of this rare disease.

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Neoadjuvant Selective RET Inhibitor for Medullary Thyroid Cancer: A Case Report

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Introduction:

In 2020 two selective RET inhibitors - selpercatinib and pralsetinib - were approved by the FDA for the treatment of advanced RET mutated medullary thyroid cancer (MTC). There is little data to support their use in other clinical contexts of MTC. Four cases of neoadjuvant therapy has been described recently. Here we present a case of neoadjuvant pralsetinib followed by surgery for a patient initially presenting with loco-regionally metastatic MTC.

Case Report:

A 47-year-old man presented with a neck lump and supra-clavicular swelling. Neck biopsy revealed cells with morphology and immuonohistochemical patterns consistent with MTC. FDG PET CT demonstrated a hypermetabolic 6 cm right thyroid tumor that merged with superior mediastinal lymphadenopathy, and a right supra-clavicular mass impinging on the right jugular vein (T4aN1bM0 Stage IV). A somatic RET C2753TC mutation was found. Serum Carcinoembryonic antigen (CEA) and calcitonin levels were 219 ng/mL (normal reference: 5.0 ng/mL) and 13,341 pg/mL (normal reference: 10 pg/mL), respectively. The patient was treated with pralsetinib at 400 mg once a day without significant side-effect, with repeat FDG PET-CT showing a partial response and decreased uptake in both tumor masses within 3 months. After 7 months of treatment, and following further response, he underwent total thyroidectomy, right neck and retrosternal dissection, revealing several viable tumor deposits in the neck and mediastinum, representing either lymph nodes completely replaced by metastasis, tumor deposits or ectopic thyroid tissue completely replaced by tumor, without any viable disease within the resected thyroid gland. Calcitonin level was 8.8 pg/mL one month after surgery. The patient was taken off pralsetinib and no further follow-up has yet been carried out.

Conclusion:

This case provides `proof-of-concept` to the feasibility of neo-adjuvant treatment with a selective RET inhibitor in sporadic metastatic Ret-mutated MTC, allowing disease shrinkage and subsequent complete resection with curative intent. Further clinical trials are required to establish the safety, efficacy, and long-term outcomes with this approach.

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Metabolic and functional factors associated with a change in resting metabolic rate among older adults with type 2 diabetes– results from the CEV-65 randomized trial

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Introduction:

Older adults with type 2 diabetes (T2DM) often struggle to achieve glycemic control due to reductions in resting metabolic rate (RMR) resulting from caloric restriction during weight loss attempts. We assessed the effects of three treatments on RMR and factors associated with changes in RMR in T2DM: circuit resistance training (CRT), a vegetarian/Mediterranean (VegMedD) diet, and the diabetes drug empagliflozin. Method: In a CEV-65 trial secondary analysis, 67 older adults (≥65 years, 61% female; mean age: 70.53+4.37) with T2DM were randomly assigned to one of three 10-week interventions (CRT, VegMedD diet, or empagliflozin). Baseline and post-10-week intervention assessments were conducted, namely, RMR measurement (dependent variable), as well as medical screening, metabolic and anthropometric measurements, nutrition assessment, and fat metabolism analysis (independent variables). Within and between-group changes in RMR were evaluated using paired t-tests, effects sizes and repeated analysis of variance. Factors associated with and predicting RMR change were also examined. Results: No significant RMR inter-group differences were observed at both baseline and post-10 weeks. The three groups also did not present statistically significant changes from baseline to week 10 in RMR with effect sizes being trivial-to-small (effect size 0.50) in both males and females. However, 16 (CRT) to 25% (VegMeD and empagliflozin) of participants experienced an RMR increase after 10 weeks. When the entire cohort was analyzed together, a total of four factors statistically significantly correlated with changes in RMR, namely, sleep hours ($r = 0.25$, $p=0.04$), changes in total body fat percentage ($r = -0.27$, $p = 0.02$), changes in maximal extension isometric leg strength ($r = 0.29$, $p = 0.01$), and changes in systolic blood pressure ($r = 0.24$, $p = 0.05$). All variables, except for systolic blood pressure predicated changes in RMR (F-ratio=7.14, $p=0.001$, R^2 adjusted = 0.22). Conclusions: In older adults with T2DM, CRT, VegMedD, and empagliflozin had comparable effects on RMR after 10 weeks. Factors predicting changes in RMR are sleep hours, fat percentage, and leg strength, with .those who increased or did not change their RMR presented greater improvement in the aforementioned variables in comparison to those experiencing a decrease in RMR. This highlights the potential of these factors as a therapeutic target for metabolic health, warranting further investigation.

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Risk factors and preventive measures for acute weight gain during military conflict in civilians with obesity

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Background

Acute weight gain during periods of heightened stress and apprehension is common in many people with obesity (PwO). We aimed to assess which factors are associated with weight gain and prevention of this phenomenon.

Methods

An online survey was sent to 2,183 subjects attending a hospital-based weight-management clinic. Between November 22nd and December 6th, 2023, 189 responses were collected during Operation Iron Swords, and 4 were excluded due to bariatric surgery within the past year. Questions topics included demographics, anthropomorphics, medical history, and the personal impact of war. We compared responses in subjects who gained significant weight (≥3%) to those who did not. Due to non-normal distribution of data, results are reported as median and interquartile range (IQR).

Results

Respondent median age was 57 (46-67) and 123 (66%) were female. Baseline BMI was 34.2 (30.4-38.8) kg/m2 and, at the time of survey completion, a median of 58 (48-58) days had elapsed since the conflict erupted. Metabolic comorbidities were prevalent and 20% reported anxiety/depression, while 6% had an eating disorder. Many were personally affected by the war, with one third being close to someone who was killed, injured, or kidnapped, and twice as many reporting worrying for a loved one on active duty. Lifestyle was also affected, with 81% endorsing a change in the circumstances of their employment, and half reporting doing less exercise had having more anxiety-driven eating. Sixty to seventy percent endorsed reduced sleep quality and increased stress/anxiety. Forty-seven respondents (25%) experienced significant weight gain with equal rates distributed across the sexes and among those who had undergone bariatric surgery (17%) vs. those that did not. Sixty-eight percent were taking weight loss medications, associated with less weight gain. Those who endorsed less exercise or anxiety-driven eating were more likely to experience weight gain (p= 0.008 and p0.001, respectively). There was a trend for an association weight gain and reduced sleep quality (p=0.059), as well as increased stress (p=0.07). According to multivariate analysis, less exercise and anxiety-driven eating associated with significant weight gain (OR=2.5, p=0.02 and OR 4.5, p0.001), while taking weight loss drugs was protective (OR=0.39, p=0.015).

Conclusion

Given that one quarter of our cohort of PwO reported significant weight gain within 60 days of the outbreak of war, this work emphasizes the importance of strategies to prevent this maladaptive pattern. While reduced exercise and anxiety-driven eating are risk factors, anti-obesity medications are protective against acute weight gain.

Table 1: Association between patient characteristics and significant weight gain during wartime

Characteristic	Overall (n=185)	No significant weight gain[†] (n=138)	Gained ≥ 3% in weight (n=47)	P value[*]
Age (years)	57 (46-67)[ᵀ]	58 (48 - 67)	54 (42 - 67)	0.20
Female sex	123 (66%)	92 (67%)	31 (66%)	
Male sex	62 (34%)	46 (33%)	16 (34%)	0.93
Current BMI (kg/m^2)	34.2 (30.1 - 38.8)	33.4 (29.5 - 39.0)	35.2 (31.3 - 38.4)	0.34
Baseline BMI (kg/m^2)	33.2 (29.8 - 39.0)	33.8 (30 - 39.0)	32.8 (29.3 - 36.2)	0.30
Taking weight loss drugs	125 (68%)	99 (72%)	26 (55%)	0.04
History of bariatric surgery	58 (48-58)	24 (17%)	7 (15%)	0.72
	Comorbidities			
T2DM / prediabetes	101 (55%)	24 (17%)	27 (57%)	0.64
HTN	66 (36%)	74 (54%)	16 (34%)	0.78
Dyslipidemia	65 (35%)	50 (36%)	20 (43%)	0.21
Fatty liver	65 (35%)	45 (33%)	17 (36%)	0.86
OSA	44 (24%)	48 (35%)	13 (28%)	0.47
ASCVD	27 (15%)	31 (22%)	8 (17%)	0.58
Depression / anxiety	36 (20%)	19 (14%)	13 (28%)	0.10
Eating disorder	11 (6%)	23 (17%)	3 (6%)	>1
	Changes during wartime			
Time since war began (days)	58 (48-58)	24 (48 -58)	58 (48 - 58)	0.72
Less exercise	95 (51%)	74 (54%)	32 (68%)	0.008
[ǂ]More anxiety-driven eating	90 (49%)	50 (36%)	36 (77%)	<0.001
Reduced sleep quality	125 (68%)	45 (33%)	37 (79%)	0.059
Rise in stress/anxiety	126 (68%)	48 (35%)	37 (79%)	0.07
Know someone injured, killed, or kidnapped	53 (29%)	31 (22%)	17 (36%)	0.18
[‡]Worried for soldiers close to me	115 (62%)	19 (14%)	30 (64%)	0.78
[ξ]Change in employment circumstances	69 (81%)	23 (17%)	17 (36%)	0.85
Started psychiatric drugs	13 (7%)	8 (6%)	5 (11%)	0.32

Legend: [ᵀ]For continuous data, median and interquartile range listed in parentheses. [*]P values reflect univariate analysis, with use of the Pearson Chi-Square Test used to assess dichotomous variables and the Mann-Whitney Test to assess continuous variables. [†]No significant weight gain – weight loss, stable or gain < 3%. ASCVD- atherosclerotic cardiovascular disease (cardiovascular, cerebrovascular, or peripheral disease); OSA- obstructive sleep apnea. [ξ]Change in employment circumstances include becoming unemployed, changing jobs, working more / less hours than before the war, or working more from home. [‡] Worried for soldiers close to me defined as respondents who answered yes to the question "Are you worried for people close to you who are serving in the military during Operation Iron Swords?" [ǂ]More anxiety-driven eating defined as respondents who answered yes to the question "As compared to period before the war, when I feel anxious, I find myself eating more."

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HYPERGLYCEMIA INDUCES CELLULAR SENESCENCE IN IDG-SW3 OSTEOCYTE LIKE CELLS

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Skeletal fragility with fractures is an emerging serious complication of type 1 diabetes (T1D) and type 2 diabetes (T2D). Hip fracture risk is up to 6-fold higher in T1D compared to age- and sex-matched non-diabetic controls and is significantly higher than in type 2 diabetes. Hip fractures occur in T1D at a younger age and their consequences are worse compared to non-diabetics. While diabetic macrovascular, brain, eye, nerve and kidney complications are widely recognized, bone fragility has received considerably less attention, even though bone fractures lead to very high morbidity and mortality. Currently available therapies to reduce fracture risk in diabetes are limited. As diabetic patients live to an older age there is an urgent need to discover new therapeutics. The underlying mechanisms of diabetes-related bone fragility are complex. At the cellular level the osteocyte appears to play a critical role. Diabetes is a condition of accelerated aging. Cellular senescence is a fundamental mechanism of aging. Senescent cells stop dividing, are resistant to apoptosis and acquire a distinct phenotype that includes secretome changes termed “senescence-associated secretory phenotype” (SASP). Clearing senescent cells was shown to improve bone status in different models of skeletal fragility in mice. In this study we asked whether hyperglycemia induces osteocyte senescence in vitro. IDG-SW3 osteocyte-like cells were cultured under 3 different conditions: normal glucose (NG; 5mM), high glucose (HG; 25mM), and mannitol 20mM with glucose 5mM (MAN), as control for the high osmolarity. Cells were harvested and the culture media was collected 0 ,3, 7, 14, 21 and 28 days post differentiation induction. Exposure to high glucose but not high osmolarity induced cellular senescence as evident by increased gene expression (4 fold) of the senescence effectors cyclin-dependent kinases inhibitors p16INK4a (CDKN2A), p21Cip1 (CDKN1A) and p53, higher P21 protein level, higher percentage of SA-β-gal+ cells, increased secreted HMGB1 in culture media. Importantly, activation of cellular senescence on HG was confirmed by proteomics analysis. Using statistically significant threshold cutoff for identifying differentially expressed proteins (DEPs), a total of 116 proteins were up-regulated and 229 were down-regulated in HG- vs. NG- but not in MAN-vs. NG-treated cells. Ingenuity pathway analysis (IPA) of DEPs showed significant enrichment for the senescence pathway with positive activation (Z=1.213; P=1.11E-05). Targeting the senescence pathway might be a novel therapeutic approach for skeletal fragility in diabetes.

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Fracture risk among children and adolescents with diabetes mellitus: a nationwide cohort study

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Background:

Impaired bone health is a known complication of diabetes mellitus (DM). Fracture risk is 2-5 fold higher among adults with DM. Data regarding fracture risk among paediatric patients are still sparse and inconclusive. We aimed to assess fracture risk among paediatric patients with DM compared with a matched comparison group.

Methods:

This registry-based cohort study included individuals who were diagnosed with DM between 2001-2020, at the age of 1-17 years. DM was identified according to the International Classification of Diseases, Ninth Revision (ICD-9) code 250. A comparison group was matched in a 5:1 ratio by age, sex, population sector and socioeconomic status. The date of DM diagnosis was used as the index-date for both groups. Clinical, laboratory and demographic data were obtained from the electronic database of Meuhedet Health Services. All fracture events since the index-date until the age of 18 or the study census date (August 31, 2023) were identified by coded diagnoses.

Results:

The DM group included 1049 individuals (52% males). The median age at DM diagnosis was 10.9 years (interquartile range (IQR) 7.5-13.4). Median HbA1c at diagnosis was 9.7 mg% (IQR 8.1-11.7). The comparison group included 5245 matched individuals. The median follow-up period of both groups was 5.5 years (IQR 3.6-8.2). We did not find a significant risk for a fracture among children with DM (adjusted hazard ratio (aHR) 1.10 for the DM group, 95% CI 0.93-1.31, p=0.25). There was increased aHR for children with celiac disease 1.46 (95% CI 1.10-1.93, p=0.009). Subgroup analysis of boys aged 11 years at DM diagnosis showed aHR of 1.47 (95% CI 1.06-2.04, p=0.02) for children with DM compared with the matched group. A multivariate analysis demonstrated that male gender (HR 2.40, 95%CI 1.36-4.25, p=0.002), and recurrent hospitalizations (HR 1.76 95%CI 1.03-3.01, p=0.04) were associated with increased risks for fractures among children with DM.

Conclusions:

We found increased fracture risk among boys aged 11 years with DM compared to a matched comparison group. Among the DM group, male gender and recurrent hospitalization were associated with increased risks for fractures.

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Novel Regulatory Role of Kidney Proximal Tubular GLUT2 in Kidney and Systemic Energy Metabolism

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Background:

Maintaining glucose homeostasis is essential for proper physiological function, and a key player in this process is the facilitative glucose transporter 2 (GLUT2). This transporter plays a pivotal role in facilitating glucose transport in metabolic organs such as the liver, pancreas, intestine, and kidney. Notably, our recent discovery underscores the protective impact of GLUT2 nullification in kidney proximal tubule cells (KPTCs) against the onset development of diabetic kidney disease in diabetic mice. Nevertheless, the influence of KPTC-GLUT2 on renal and systemic metabolism under normo-physiological conditions remains unexplored.

Methods:

Throughout this study, we conducted a comprehensive examination into the consequences of GLUT2 nullification specifically within KPTCs on both renal and systemic energy metabolisms under normo-physiological conditions. Employing a multidisciplinary approach that included kidney semi-targeted metabolomics profiling, molecular biology techniques, as well as metabolic cages and PET-MRI, we sought to provide a thorough understanding of the observed effects.

Results:

We provide evidence that the targeted nullification of KPTC-GLUT2 in mice, under normo-physiological conditions, led to the accumulation of glucose in KPTCs, thereby augmenting kidney energy metabolism. Simultaneously, this alteration affected systemic carbohydrate uptake and utilization across various organs, accompanied by an enhancement in the overall lipid profile of the entire body. These metabolic changes were intricately linked to a reprogramming of metabolism within the kidney, resulting in modified bioavailability and reabsorption of taurine, with systemic implications.

Discussion:

Our findings offer valuable insights into the systemic metabolic benefits stemming from the modulation of glucose reabsorption in the kidney, particularly through the elevation of taurine levels both locally and systemically. These findings contribute novel perspectives on the therapeutic potential of targeting KPTCs metabolism to address diabetes and obesity, illuminating potential avenues for future therapeutic interventions.

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To count or not to count? Simplified carbohydrate estimation superior to precise counting with AHCL

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Background:

We aimed to compare glucose control in adults with T1D using the MiniMed 780G AHCL system when using simplified meal announcement versus precise carbohydrate counting.

Methods:

In a single-arm study involving 14 adults with T1D, we evaluated glycemic control during a 13 week "precise phase", where patients counted all carbohydrates (CHOs) followed by two 3-4 week simplified meal announcement phases: the "universal" phase (preset of one personalized fixed carbohydrate amount) and the "incremental" phase (1-3 multiples of preset depending on CHO content).

Results:

Mean age was 45.7±12.4 years and ten participants were male (71%). Baseline HbA1c was 6.8%±1.2% and time in target glycemic range (TIR) 67.5%±16.7%. There were no serious adverse events. Between study phases there were no differences in the frequency of postprandial hyperglycemia requiring intervention per protocol.

While the number of announced meals during study phases were similar, compared to the precise phase, less CHOs were announced in the universal and incremental phases, (106.4±30.4 g vs. 193.3±71.3g, p0.001) and (144.0±59.2g vs 193.3±71.3, p=0.001), respectively. In accordance, compared to the precise phase, total daily insulin dose (TDD) was lower in the incremental phase (40.7±20.5 vs. 45.4±23.9, p=0.04), with a trend toward a lower TDD in the universal phase (40.3±21.7 vs. 45.4±23.9, p=0.08).

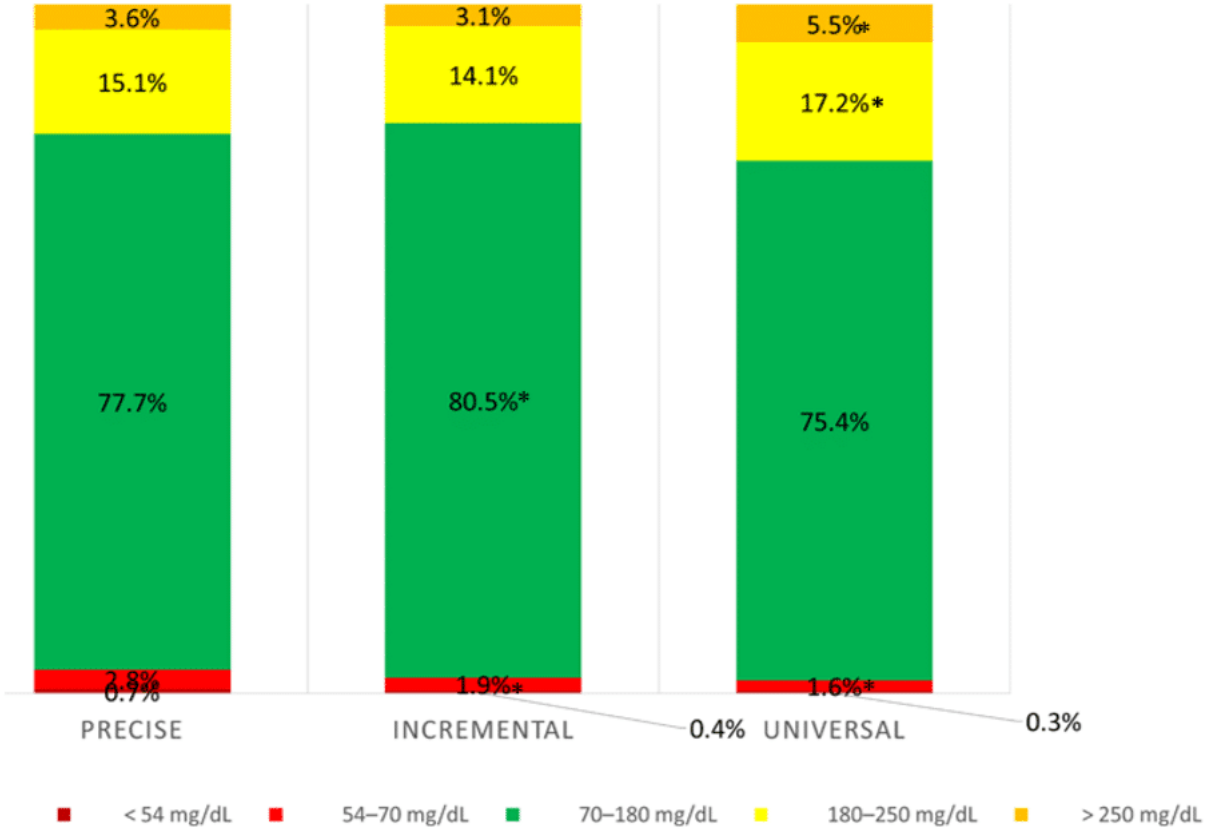
Despite a lower TDD in the incremental than the precise phase, GMI was identical (6.6%) and TIR was superior (80.5±10% vs. 77.7±9%, p=0.02). Additionally, there was less mild hypoglycemia (1.9±1% vs. 2.8±2%, p=0.01), a trend for less moderate hypoglycemia (0.4±0.7% vs. 0.7±1%, p=0.08), and less glycemic variability as assessed by CV (32.1±6.5 vs. 34.6±5.9%, p=0.03).

Even when comparing the universal to the precise study phase, there was no difference between TIR (75.4±13% vs. 77.7±9%, p=0.12), and GMI was only slightly higher (6.8±0.4 vs. 6.6±0, p=0.01). Additionally, there was less mild hypoglycemia (1.6±1% vs. 2.8±2%, p=0.03), with a trend for less moderate hypoglycemia (0.3±5% vs. 0.65±1%, p=0.08). There was more level 1 and 2 hyperglycemia (17.1±8% vs. 15.0±7%, p=0.05 and 5.5±5% vs. 3.6±3%, p=0.04). CV was nearly identical between study phases (34.4± 6.6 vs. 34.6±5.9).

Conclusions:

A simplified bolus strategy in adults using AHCL, relying on 3 multiples of a universal bolus depending on CHO estimation, may a novel way to simultaneously improve control while reducing the burden of diabetes self-care. For patients with more limitations, using one universal bolus can be weighed given that this approach is safe and meets nearly all consensus glycemic targets.

Figure 1: Comparison of percent time in ranges of sensor glucose in study phases



* p<0.05 compared to precise phase

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Mid-aged mice normalize obesity-induced dysglycemia during weight loss along with aggravated hypothalamic inflammation: Implications to mid-age weight cycling and neurodegenerative disorders?

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Background:

Rodent models of dietary obesity have uncovered multiple insights concerning the process and impact of becoming obese, particularly in young mice, corresponding to the post-pubertal phase in humans. Yet, most common human-clinical scenarios deal with the need to improve health by weight loss during mid-age. To address this gap, we have been studying the relative dynamics of the reversal of obesity-induced changes early during weight-loss, comparing young and mid-aged mice. Hypothesis: Here we hypothesized that older mice would reverse glycemic and hypothalamic changes (transcriptional and cellular-microglial) slower/less than young mice early in the course of obesity reversal. Methods: We compared 2m-old (young) and 1y-old (mid-aged) mice during a 10w diet intervention, comprised of 8w high-fat-diet (60% fat, HFD) consumption, followed by 2w normal-chow (NC) intake. We documented weights, performed an intraperitoneal glucose tolerance test (GTT), and at the end of the 10w diet regimen, extracted hypothalami for bulk-RNA sequencing and confocal analysis. Results: Although mid-aged mice gained lower weight compared to young mice, both groups fully reversed dysglycemia one week after switching from HFD back to NC. Two weeks into the dietary switch, after losing 67% and 58% of their excess body weight, hypothalami bulk-seq revealed 670 and 2400 differentially expressed genes in young and mid-aged hypothalami, respectively, when compared to its age-matched lean control. Mid-age brains showed more robust enrichment in pathways of neurodegenerative diseases and metabolic pathways compared to young mice, and most genes (~80%) exhibited an aggravation pattern, instead of reverse, upon acute weight loss. In the obese state, both groups exhibited increased microglia cell number and volume, changes that were most evidenced in the arcuate nucleus. In response to weight loss, there was only a non-significant reversal to the homeostatic pattern of microglia phenotype in young mice. Remarkably, mid-aged mice exhibited a seemingly paradoxical increase in microglial number, cell volume, and pNFkB+ microglia beyond the increase observed between obese and lean mice, corresponding to transcriptomic changes. Summary/conclusions: Contrary to our hypothesis, mid-aged mice exhibited remarkable peripheral metabolic flexibility upon early weight loss, similar to young mice. Nevertheless, weight loss not only did not reverse but in fact was aggravated, to a higher extent in mid-age vs young mice, in terms of hypothalamic transcriptional and microglial changes in the arcuate nucleus.

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Germline DNA methylation analysis reveals distinct alterations in a large cohort of patients with germline SDHB pathogenic variant

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Patients with germline pathogenic variant (PV) in the SDHB gene (Paraganglioma syndrome type 4, PPGL4) have a high-risk of developing paragangliomas and pheochromocytomas. PPGL4 has increased risk for aggressive and metastatic abdominal-thoracic paragangliomas compared with other paraganglioma syndromes.

Aims:

To assess possible germline DNA epigenetic alterations in patients harboring the SDHB PV.

Materials and Methods:

Patients with PPGL4 were characterized clinically in our clinic and genetically via germline DNA sequencing for the familial variant (SDHB c.640CT p.Q214Ter, n=144) and whole genome methylation analysis compared 19 patients vs. 129 controls. The control group consisted of four SDHB PV-negative family members and 125 samples retrieved from a public database (GSE224359). Analysis was performed on Rstudio, using the ChAMP suite for normalization, imputation, differentially methylated probes (DMP), and regions (DMR) analyses. Pathway analysis and visualization were executed using the clusterprofiler and enrichplot packages. Promoter regions were defined by the transcription start site (TSS1500).

Results:

The cohort includes three kindreds, presenting independently with an index patient: Index patient in kindred A, a 12-year-old boy, with thoracic paraspinal and testicular paragangliomas. Index patient in kindred B, a 26-year-old woman with abdominal paraganglioma, metastatic to the lungs and spine. Index patient in kindred C, a 41-year-old man with a locally aggressive abdominal paraganglioma, metastatic to the skull and spine. A total of 114 (44.2% females) patients underwent genetic evaluation (45/50, 16/28, and 25/36 in kindreds A, B and C, respectively). Of those, 50 (58.1%) harbored the familial SDHB PV (68.9%, 56.2%, and 40.0%, respectively). Twenty-six patients underwent at least partial clinical evaluation: eight had paraganglioma (4/8 had metastatic disease), three had pheochromocytoma, and two patients had neck masses that are currently being evaluated.

Based on germline DNA promoter methylation data, SDHB PV carriers clustered separately from controls, including the SDHB PV non-carriers from the same kindred. No separation was demonstrated between patients that developed vs. not developed PPGL at the time of the data collection. CpGs annotated to multiple genes were found differentially methylated between the groups. Of special interest are MGMT (encoding methyl guanine O-methyl transferase), and ARID1B (encoding AT-rich interactive domain-containing protein 1B) in the SDHB PV positive group.

Conclusions:

We report one of the largest cohorts of PPGL4, showing typical low penetrance and aggressive phenotype. Genomic analysis shows distinct germline DNA methylation in SDHB PV-positive compared with the control group. Future studies may reveal an association between specific epigenetic alterations and penetrance/phenotypic patterns.

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Incidence, temporal trends, and socioeconomic aspects of male hypogonadism

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Background:

Hypogonadism, for any reason, can affect libido, quality of life, cardiovascular risk factors, morbidity, and mortality. Besides improving libido and sexual function, evidence has emerged that testosterone therapy has significant cost-effective health benefits on multiple health parameters, quality of life, and overall survivability. Awareness of the epidemiology of hypogonadism, targeted detection, and appropriate treatment may improve men`s quality of life, general health status, and life expectancy and reduce healthcare expenses. There is little data about temporal changes in the incidence of definite hypogonadism and its correlation with socioeconomic status.

Methods:

We extracted data from the Maccabi Health Services computerized database between 2001 and 2017, which includes all electronic health records and laboratory data. The study included 4261 men with biochemically verified hypogonadism defined according to the European Male Study criteria. We excluded patients already treated with testosterone-modifying drugs (testosterone, anabolic agents, selective estrogen-receptor modifiers, clomiphene) or those undergoing gender-reaffirmation procedures.

Results:

Male hypogonadism increased persistently with age in all the socioeconomic strata. 75% of the hypogonadal men had hypogonadotropic hypogonadism. The overall incidence of hypogonadism increased 1.4-fold between the 2001-2009 and 2010-2017 periods, mainly due to an increase in hypogonadotropic hypogonadism. The temporal increase in hypogonadism occurred in all age groups of all socioeconomic strata but was notably more prominent in the 51 age group of the more affluent socioeconomic strata. BMI remained unchanged throughout the study period.

Limitations:

The data are retrospective and extend over a long period; we had no access to individual patient clinical data on hypogonadism symptoms and erectile dysfunction. Testosterone screening is not routinely performed; thus, we can only assume that testosterone testing was performed based on clinical complaints.

Discussion:

The observed temporal increase in hypogonadism corresponds with previous observations of a secular decrease in testosterone levels in men of a yet undetermined cause(s). The predominance of hypogonadotropic hypogonadism could be hypothetically linked to an underappreciated association between hypogonadotropic hypogonadism and mental distress due to workplace demands and occupational burnout observed with more affluent populations in specific occupations (i.e., high-tech, finance, medical) reflected by decreased global happiness indices. This preliminary proposition deserves further investigation.

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The relationship between neonatal hypoglycemia and glucose control during labor of mothers with type 1 diabetes

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Introduction:

Neonates of women with type 1 diabetes (T1D) are at increased risk for neonatal hypoglycemia. It is hypothesized that avoiding intrapartum maternal hyperglycemia and maintaining glucose between 70-110 mg/dl according to ACOG or 63-140 mg/dl according to ADA, may prevent fetal hyperglycemia and reduce the likelihood of subsequent neonatal hypoglycemia.

Aim:

To test for association between clinically significant neonatal hypoglycemia (requiring IV glucose treatment) and intrapartum glucose control.

Materials and methods:

This is a prospective cohort study of women with T1D followed at a single tertiary center. Clinical variables, intrapartum glucose control and neonatal glucose were recorded. The correlation between clinically significant neonatal hypoglycemia and intrapartum glucose control was determined.

Results:

Seventy-six pregnant women and their newborns were included in the study. Twins' pregnancies were excluded from analysis. Mothers whose neonates did not experience significant hypoglycemia exhibited superior intrapartum glucose control, as evidenced by higher time in range (TIR%) within the 63-140 mg/dl range, and lower time above range (TAR%) both 24 hours and 1 hour before labor (76% vs. 63%, p=0.01), (16% vs. 27%, p=0.05), (82% vs. 61, p=0.01) and (14% vs. 35%, p=0.03) respectively, compared to those whose neonates experienced hypoglycemia. No significant differences were observed in time below range 63 (TBR%) either any of glucose control indices between the two groups using the range 70-110 mg/dl.

Conclusion:

The study supports the hypothesized association between enhanced intrapartum glucose control in mothers with T1D, specifically maintaining glucose levels within the range 63-140 mg/dl, and diminished likelihood of clinically significant neonatal hypoglycemia.

keywords: neonatal hypoglacemia, type 1 diabetes, intrapartum glucose control

Indices summarizing the glucose measurements within 24H before labor

	Significant Neonatal hypoglycemia	No significant Neonatal hypoglycemia	P*
TIR (63-140) (%)	0.63	0.76	0.01
TBR1 <63 (%)	0.10	0.08	0.94
TBR2 <54(%)	0.06	0.03	0.43
TAR1>140(%)	0.27	0.16	0.05
TAR2>180(%)	0.08	0.03	0.07
Mean	114	107	0.15
SD	35	30	0.03

TIR- time in range, TAR- time above range, TBR- time below range

Indices summarizing the glucose measurements within 1H before labor

	Significant Neonatal hypoglycemia	No significant Neonatal hypoglycemia	p
TIR (63-140) (%)	61	82	0.01
TBR1 <63(%)	5	3	0.38
TBR2 <54(%)	3	1	0.30
TAR1 >140(%)	35	14	0.03
TAR2>180(%)	5	2	0.46
Mean	121	112	0.21
SD	7.8	7.5	0.72

TIR- time in range, TAR- time above range, TBR- time below range

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Possible association between promoter methylation level of genes encoding catecholamine metabolizing enzymes and metanephrine secretion in pheochromocytoma and paraganglioma

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Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors that may secrete catecholamines and their metabolites (metanephrines [MN], normetanephrine [NMN]). Secretion patterns differ by adrenal/extra-adrenal origin and genetic alteration. Catecholamines synthesis is carried by phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), dopamine β-hydroxylase (DBH) and phenylethanolamine N-methyltransferase (PNMT). However, their regulation in PPGL is not entirely understood.

Objective Assess whether epigenetic gene regulation of catecholamines synthesizing enzymes leads to distinct MN and NMN secretion patterns in PPGLs.

Methods:

PPGL methylation data from 178 samples were collected from a public database. We analyzed the methylation of CpGs of PAH, TH, AADC, DBH, and PNMT and compared MN and NMN secretion by methylation levels. We also compared methylation levels by genetic alteration subgroups (pseudohypoxia [PH], kinase signaling [KS]).

Results

Methylation of PAH and DBH CpGs negatively correlated with probability for MN/NMN secretion (p0.05 for PAH CpGs) but positively correlated with NMN-only secretion, with similar trends for TH, PNMT, and DDC. NMN-only secreting tumors had significantly higher promoter methylation of PAH, DBH, and PNMT, compared with MN/NMN secreting tumors. Comparison by genetic alteration demonstrated that tumors with PH alterations had relative hypermethylation of the gene promoters of PAH (p=0.002), DBH (p=0.02), and PNMT (p=0.003) compared with KS.

Conclusions

Promoter methylation of genes encoding for catecholamine synthesis enzymes is strongly and inversely associated with MN/NMN secretion patterns in PPGLs. KS and PH-related tumors are associated with distinct methylation patterns. This implies that methylation is a key regulatory mechanism of PPGLs catecholamines secretion.

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First-trimester fasting plasma glucose levels and progression to type 2 diabetes: A 5-Year Cohort Study.

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Introduction:

Impaired fasting glucose is a prediabetic condition defined as glucose levels of 100-125mg/dl and is considered a risk factor for type 2 diabetes mellitus. However, this definition doesn't confer to pregnancy. The significance of 1st-trimester fasting glucose and future progression to diabetes is not well defined. In this study, we aimed to evaluate the progression to type 2 diabetes according to 1st- trimester fasting plasma glucose levels, as compared to gestational diabetes, a well-established risk factor for diabetes, in up to 5-year follow-up after pregnancy.

Material and Methods:

A retrospective analysis was conducted on 69,001 parturients, evaluating fasting plasma glucose levels measured during the first trimester. The primary outcome was the incidence of type 2 diabetes within 5 years post-delivery. Fasting plasma glucose levels were categorized in 10 mg/dl increments. ROC-AUC statistics and the Youden index were employed to identify the optimal fasting plasma glucose cutoff for progression to type 2 diabetes. Survival analysis was applied to calculate the adjusted hazard ratios (aHR) for type 2 diabetes progression with further stratification to maternal obesity status.

Results:

The identified fasting plasma glucose cutoff for progression to type 2 diabetes was 86.5 mg/dl (sensitivity 53.3%, specificity 72.4%). This cutoff demonstrated superior performance compared to gestational diabetes diagnosis (0.61 vs. 0.58). Additionally, all fasting plasma glucose levels exceeding 80 mg/dl were associated with an increased risk of developing type 2 diabetes. Levels equal to or greater than 110 mg/dl exhibited a higher risk compared to gestational diabetes diagnosis (aHR 4.92 and 3.92, respectively). Stratification by maternal obesity revealed enhanced predictive capabilities for type 2 diabetes, particularly among patients without obesity.

Conclusions:

Increased 1st-trimester fasting plasma glucose levels are associated with progression to type 2 diabetes, at least as gestational diabetes. For patients without obesity, 1st-trimester fasting plasma glucose has a more pronounced impact on progression to diabetes and should be considered when adapting postpartum recommendations.

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Timing of Gestational Diabetes Diagnosis and Progression to Type 2 Diabetes: A Comparative Analysis

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Aim:

To evaluate and compare the risk of progressing to type 2 diabetes mellitus (T2DM) based on the timing of gestational diabetes (GDM) diagnosis during pregnancy.

Methods:

Retrospective analysis of pregnant individuals with up to 5 years of post-pregnancy follow-up. Data sourced from Meuhedet HMO`s computerized laboratory system, cross-tabulated with the Israeli National Diabetes Registry. Exclusions: multifetal pregnancies, prior T2DM diagnosis, fasting plasma glucose 125mg/dL in 1st trimester. The cohort was divided into normoglycemic, early GDM (diagnosed by fasting plasma glucose 92-125mg/dL at 15 weeks), on-time GDM (diagnosed at 24-28 weeks), and late GDM (diagnosed after 29 weeks). Maternal characteristics, obstetrics data, and T2DM were stratified by the timing of GDM diagnosis. Risk was further analyzed for individuals by obesity status. Statistics included univariate analysis followed by survival analysis.

Results:

75,459 entered the analysis: 90% normoglycemic, 7.9% early GDM, 1.4% on-time GDM, and 0.7% late GDM. On-time GDM showed the highest T2DM risk annually after pregnancy. Kaplan-Meyer curves indicated increased T2DM risk for all GDM cases, with on-time GDM having the highest risk. Cox regression, adjusted for confounders, revealed a significantly higher T2DM risk for on-time GDM compared to early and late GDM. Late GDM did not confer additional significant T2DM risk. Stratification by obesity status highlighted the remarkably elevated risk of on-time GDM in individuals without obesity. Moreover, early GDM increased the risk of T2DM only in individuals without obesity.

Conclusions:

GDM diagnosis timing significantly impacts T2DM risk within 5 years. On-time GDM carries the highest T2DM progression risk.Early GDM is linked to an elevated T2DM risk particularly among patients without obesity.

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Frequency of MC4R Pathway Variants in an Israeli Cohort of Individuals with Early-Onset Severe Obesity

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Background:

Monogenic obesity is a rare form of obesity resulting from pathogenic variants in genes implicated in the leptin–melanocortin signaling pathway (MC4R pathway). The MC4R pathway is crucial for regulating satiety, energy balance, and body weight. Abnormalities in the MC4R pathway are characterized by early weight gain, hyperphagia, and severe obesity.

Objective:

To elucidate the genetic causes of early-onset obesity in severely obese children younger than 21 years, referred to the pediatric endocrinology clinic at Sheba Medical Center, Israel.

Methods:

The study group comprised 140 children with early-onset obesity. A targeted gene panel, comprising 80 obesity-related genes, was used for screening, as part of the genetic testing program of Rhythm Pharmaceuticals, Inc.

Results:

Among the cohort, 69 (49.3%) exhibited 97 gene variants. Twenty-one (30%) carried two variants, and two carried 3 different gene variants. Of these 33% were classified as benign, 8% as pathogenic or likely pathogenic, 24.7% as suspected pathogenic, and 34% as uncertain. Thirty-two distinct genes were identified, with PCSK1 (10%), MC4R (7%), PLAXNA1 (7%), and TBX3 and MRAP2 (5% each) being the most common. Other genes included SH2B1, POMC, PLXNA4, DYRK1B, KIDINS220, MC3R, NRP1, PLAXNA2, PLXNA4, SEMA3D, SEMA3F. No significant BMI Z score difference was observed between those with positive gene variants and those with negative results.

Conclusion:

Approximately one-third of our cohort exhibited pathogenic/suspected pathogenic variants that appear to account for the phenotype. With the innovative treatment in the MC4R pathway incorporating genetic testing into the clinical care of individuals with severe obesity, is important as the degree of obesity is not a reliable indicator.

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Flat oral glucose tolerance test during pregnancy and risk for type 2 diabetes – a five-year cohort study

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Objectives:

To evaluate the risk of type 2 diabetes mellitus (T2DM) in women with flat response in the 100-gram oral glucose tolerance test (OGTT) performed during pregnancy in a large cohort of women with up to 5 years of follow-up.

Methods:

A retrospective analysis of women with documented glucose values during pregnancy and T2DM data up to 5 years after pregnancy. Gestational diabetes (GDM) screening was done by two-step strategy. Glucose levels during pregnancy were extracted from the computerized laboratory system of Meuhedet HMO and cross-tabulated with the Israeli National Diabetes Registry. Flat OGTT was defined as fasting glucose 95mg/dl and 3 postprandial values lower than 100mg/dl. The cohort was stratified by OGTT results to normal glucose values, flat OGTT, and GDM according to Carpenter & Coustan thresholds. Cumulative risk for T2DM was evaluated and compared between groups. Statistical analysis included univariate analysis followed by survival analysis.

Results:

14,122 parturients entered analysis. Of them, 965(6.8%) had flat OGTT, 11,427(80.9%) had normal OGTT, and 1,730(12.3%) had GDM. Women with flat OGTT were younger, had lower BMI, and lower rates of hypertension. Their glucose values throughout pregnancy were lower compared to the other groups (p0.001 for all). During the study period and following adjustment to maternal age, obesity, and hypertension, women with flat OGTT had a low incidence of T2DM, even compared to women with normal OGTT (aHR 0.212, 95% CI 0.052-0.856).

Conclusion:

Parturients with flat OGTT during pregnancy are at low risk of developing T2DM up to 5 years following pregnancy.

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Gestational diabetes in multiple pregnancies and risk for type 2 diabetes mellitus – a 5-year cohort study

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Objective:

This study aimed to assess the risk of GDM progression to T2DM in a large cohort of pregnancies with a 5-year follow-up, comparing singleton and multiple pregnancies.

Methods:

A retrospective analysis was conducted on a prospective cohort of women with pregnancies between January 1, 2017, and December 31, 2020, followed up to five years after delivery. Glucose levels during pregnancy were obtained from the Meuhedet Health Maintenance Organization laboratory system and cross-linked with the Israeli National Registry of Diabetes. The cohort was divided into four groups: singleton without GDM, singleton with GDM, multiple without GDM, and multiple with GDM. GDM was defined according to the American Diabetes Association criteria using the two-step strategy. Univariate analyses, followed by survival analysis that included Kaplan-Meier hazard curves and Cox proportional hazard models were used to assess differences between groups and calculate the adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for progression to T2DM.

Results:

Among 88,611 parturients, 61,891 cases met the inclusion criteria. The prevalence of T2DM was 6.5% in the singleton GDM group and 9.4% in the multiple GDM group. Parturients with GDM, regardless of plurality, were older and had higher fasting plasma glucose levels in the first trimester. Rates of increased BMI, hypertension, and earlier gestational age at delivery were significantly higher in the GDM group among singletons but not among multiples. Survival analysis demonstrated that GDM was associated with aHR for T2DM of 4.62 (CI 3.69-5.78) in singletons and 9.26 (CI 2.67-32.01) in multiples (p0.001 for both). Stratified analysis based on obesity status revealed that in parturients without obesity, GDM in singleton pregnancy increased the risk of T2DM by 10.24 (CI 6.79-15.44, p0.001) compared to a non-significant risk in multiples (aHR of 9.15, CI 0.92-90.22, p=0.059). Among parturients with obesity, GDM was associated with increased risk of T2M for both singletons and multiples (3.66 (2.81-4.67) and 9.31 (2.12-40.76), aHR(95%CI), p0.001 and p=0.003, respectively).

Conclusion:

GDM in multiple pregnancies doubles the risk of progression to T2DM compared to singleton pregnancies. This effect is primarily observed in patients with obesity. These findings underscore the importance of providing special attention and postpartum follow-up for patients with multiple pregnancies and GDM, especially those with obesity, to enable early diagnosis and intervention for T2DM.

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Adipose tissue histopathology as a putative basis for advancing personalized management of obesity

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The etiology of the obesity pandemic is unsettled. However, the tendency of obesity to be complicated by cardiometabolic Adiposity-Based Chronic Diseases (ABCD) appears to be associated with the adaptation of adipose tissue to chronic caloric surplus. This realization is mainly based on cross-sectional studies, in which adipocyte size, adipose tissue fibrosis and inflammation may segregate with complicated obesity. Though with some support, a major gap of knowledge is whether such parameters can be predictive of the future development of ABCD and/or the response to treatment. To address this gap of knowledge, we have begun to generate a database of histopathological features of subcutaneous and visceral (omental) adipose tissues collected during elective abdominal surgeries (mostly bariatric/metabolic), complementing clinical characteristics we have been collecting in our adipose tissue biobank. In addition, we have recently initiated structured follow-up visits aimed at assessing anthropometric and biochemical parameters from 6 months- 5 years post-operatively. We aim to present cross-sectional analyses of associations between clinical parameters and adipose tissue features: i. adipocyte size (based on which obesity can be categorized as “hypertrophic” or “hyperplastic”); ii. degree of fibrosis (total fibrosis), and iii. immune-cell abundance (macrophages, crown-like structures, mast cells). As of March 2022, sixty participants (75% women) were enrolled, and histopathological evaluation of their adipose tissue samples was executed. The median age was 40 (range 20-69), and median BMI was 44 (range 30-61). In 14 (23%) participants the samples were taken during a second bariatric/metabolic operation (mainly conversion of gastric banding to bypass procedures). Follow-up data of 6 months and one year are currently available for 8 and 17 participants, respectively. Adipocyte area was smaller in visceral adipose tissue (VAT) as compared with subcutaneous adipose tissue (SAT) (5688μm^2 versus 7317μm^2, p0.0001, respectively). A sex-based difference was demonstrated in the VAT depot where adipocytes area was smaller in men than in women (5405μm^2 versus 6540 μm^2, p= 0.03, respectively). Total fibrosis in VAT was positively correlated with age (r=0.5456, p0.0001), and negatively correlated with BMI (r=-0.5232, p=0.0002).

In summary, we report initial results of a setup aimed at exploring whether routine histopathological evaluation of adipose tissue could improve sub-phenotyping of persons living with obesity, and enhance personalizing the approaches to reduce cardio-metabolic risk and improve outcomes of anti-obesity interventions.

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The impact of Meal Bolus Timing on Postprandial Glucose Control with AHCL system: A Prospective Repeated Measure Study

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Objective:

Achieving optimal postprandial glucose control is a primary goal in the management of type 1 diabetes. While it is recommended to deliver insulin prior to the meal for a tighter glucose control, not all people adhere to this practice for various reasons. The announcement of meals in conjunction with Advanced Hybrid Closed Loop (AHCL) systems, plays a pivotal role in determining post-meal glucose excursions. The aim of this study was to evaluate the criticality of meal bolus timing with the Medtronic MM780G by assessing the effect of different meal bolus timing on postprandial glucose levels following a medium-sized meal.

Method:

Thirteen individuals with type 1 diabetes, aged 42.8±13.6 years, and a baseline hemoglobin A1c of 6.9±0.67%, participated in this study. Participants completed a series of meal tests, each representing one of the four bolus timing strategies:1) 10-minutes pre-meal, 2) at the beginning of meal, 3) reduced bolus by 50% delivered 30 minutes post- meal, 4) reduced bolus by 50% delivered 60 minutes post-meal.

Result:

Results showed that bolusing at the meal`s outset yielded a comparable Time in Range (TIR) compared to the 10-minute pre-meal bolus approach (82.2% vs. 77.4%, p=0.5), while significantly reducing the time spent in hypoglycemia (p=0.016)

Conclusion:

These findings underscore the potential of AHCL systems utilizing real-time sensor glucose measurements to eliminate the need for pre-meal bolusing, thereby enhancing postprandial glycemic control and alleviating the burden on individuals managing type 1 diabetes. This research sheds light on innovative approaches to optimize glucose management.

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Overweight and obesity in survivors of childhood cancer

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Background:

Multiple studies demonstrated increased incidence of obesity, as well as of associated morbidity, including the metabolic syndrome and cardiovascular morbidity in childhood cancer survivors (CCS). Still, data regarding the rates and the timeline of obesity as well as of specific risk factors are inconsistent.

Aim:

To evaluate the rate of overweight and obesity in CCS, to characterize longitudinal changes in weight status, and to identify predictors of obesity in this population.

Methods:

A retrospective cohort study, comprising of all patients followed at the endocrine late effects of childhood cancer clinic between 1.1.2000 – 31.12.2020, diagnosed between the ages of 0-18 years, with follow-up of at least one year following completion of anti-cancer treatment. Pertinent data were abstracted from the patients` medical charts.

Results:

The final study cohort included 820 CCS (males:473, 57.7%). The mean age at the time of oncological diagnosis was 7.1±5.1 years, with a median follow-up of 5.5 years from diagnosis. At their last clinic visit, 15.6% of survivors were overweight and 11.1% of them were obese. Compared to the general population, we observed higher rates of overweight and obesity in CCS in males aged 2-6 years (33% vs. 14%, p0.001), in males aged 6-12 years (38% vs. 19%, p0.001) and in females aged 6-12 years (35% vs. 21%, p0.001). Multivariate analysis identified weight status at the time of diagnosis (p0.001), and endocrine dysfunctions (OR=1.46, 95%CI 1.08-1.98, p=0.01), as independent predictors of overweight and obesity. The highest rates of overweight and obesity were observed 3-5 years after diagnosis (OR=1.3, 95% CI 1.11-1.53, p=0.001). Diagnosis between the ages 10-14 years, was associated with lower odds of overweight and obesity at the end of follow up compared to diagnosis at an age younger than three years (OR 0.51, 95% CI 0.32-0.83, p0.01). There was no association between weight status at the last visit and gender or type of oncological disease. There was a significant increase in BMI-SDS up to 5 years after diagnosis (0.067±0.033, p=0.04), followed by a decrease in BMI-SDS with a later follow up of 5-10 years (-0.11±0.037, p=0.002), and more than 10 years after diagnosis (-0.25±0.055, P0.001).

Conclusion:

Weight status at diagnosis, endocrine deficiencies, and length of follow-up were identified as predictors of overweight and obesity in CCS. Our results may help in identifying at-risk patients and in designing appropriate targeted interventions that might decrease obesity and related morbidity in CCS.

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D2 Agonists as first line therapy for nonfunctioning pituitary macroadenoma - A single center experience

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Background:

D2 agonists (D2A) have been shown to decrease rates of post-surgical remnant growth in nonfunctioning pituitary macroadenomas (NFPMA). The role of primary medical treatment of NFPMA is less validated.

Aim:

To report our experience with D2A as primary medical treatment for NFPMA.

Methods:

We retrospectively studied 30 surgery naïve patients harboring NFPMA. Patients were divided into those with and without primary medical therapy with D2A. Clinical and biochemical parameters were collected from the electronic medical records. MRI images were used to assess tumor volume at baseline and the end of follow-up using the Livewire Carestream PACS software. Distance from the chiasm was measured in mm. A change of 10% in tumor volume and 2 mm or more in the distance from the chiasm were considered as significant.

Results:

The average age at diagnosis of NFPMA in the D2A group (n=22) and the control group (n=8) was 66.5±11.8 and 52.6±20.3 years, respectively. Females comprised 63.6% of the D2A group and 62.5% of controls. Headache was reported by 62.5% in the D2A group and 54.5% of controls. Visual field defects were observed in 9% of the D2A group and 12.5% of controls. Rates of any pituitary hormone deficiency were 13.6% in the D2A group and 12.5% in controls.

Mean baseline tumor volume was 3423 mm3 in the D2A group and 1670 mm3 in controls. Mean cabergoline dose was 1.7 mg/week. Median follow-up duration was 65.2 months (range 11-182) for the D2A group and 57.5 months (range 9-103) for controls. In patients receiving D2A, tumor volume decreased in 50%, increased in 22.7%, and remained unchanged in 27.2%. In the control group, these rates were 28.5%, 28.5%, and 42.8% respectively. The distance between the tumor and the optic chiasm increased in 18% of patients in the D2A group, compared to 14% in the control group, and decreased in 0% compared to 28%, respectively. Over the follow-up period, 31% of patients receiving D2A underwent surgery due to tumor growth (n=4) apoplexy (n=2), and persistence of headache (n=1). Two patients (25%) from the control group had surgery for impaired visual fields (n=1) and tumor growth (n=1).

Conclusions:

In our cohort of patients with NFPMA, primary treatment with D2A decreased and or stabilized tumor volume to a greater extent compared to no treatment, and about 70% did not need surgery. Further long-term assessment of this medical treatment approach for NFPMA is needed.

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Unifying regulatory motifs in endocrine circuits

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In this study we identify unifying design principles in human endocrine systems. We find that 43 hormone systems, controlling diverse physiological functions, fall into just 5 classes of circuits with shared structure - thus only a very small number of the possible circuits actually appear. Each class uses a different regulatory logic to perform specific dynamical functions, such as homeostasis, acute input-output response or adjustable set points. The circuits employ interactions on two timescales: hormone secretion on the scale of minutes-hours and growth and shrinkage of endocrine gland mass on the scale of months, which impacts the amount of hormone the glands secrete. This two-timescale principle recurs in several classes of circuits, including the most complex class, which has an intermediate gland, the pituitary. We analyze the pituitary circuit in detail and find tradeoffs between endocrine amplification, buffering of hypersecreting tumors, and rapid response times. These unifying principles of regulation build a foundation for systems endocrinology.

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Hot Flashes are Associated with Text-Based Markers of Cognitive Impairment: Observational Study of Posts on Social Media

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Background:

Cognitive complaints are common during the menopause transition, predominantly encoding and recall of words, termed verbal memory. Estrogen receptors are abundant in the hippocampus and prefrontal cortex, suggesting direct estrogen involvement in cognition. The contribution of CNS-manifestations of hot flashes, disturbed sleep and mood to cognitive impairment is yet unknown. Social media groups offer an unprecedented large data source for studying subjective experiences alongside objective cognitive analysis using validated text-markers.

Objective:

To evaluate parameters of cognitive function and their association with hot flashes.

Methods: Reddit posts (from 2011-2022) from the menopause group and a control group of women aged 45-60 in Reddit's general-medical questions group were studied. 338 menopause group posts were labeled for relevant topics (menopause, hot flashes, cognitive issues, mood, sleep, and age) and used to train a machine learning model, which predicted labels for the remaining posts. Cognitive function parameters, such as text length and percentage of unique words, were analyzed for both groups` users.

Results:

The menopause group comprised 2387 women, generating 167798 posts across Reddit, the control group included 3710 women. Average age in the menopause group was 44.3 years (range: 21-59, N=165). Hot flashes were reported in 41%, adverse mood 21%, impaired sleep 10% and cognition in 2%. In women with hot flashes, adverse mood occurred in 59.5%, impaired sleep 46.3% and cognition in 11.1%. In women without hot flashes adverse mood occurred in 10%, impaired sleep 2.4% and cognition in 1%.

The likelihood that a post was predicted to contain a complaint about cognitive function was correlated with text length (Spearman rho=0.21, P0.01) and inversely with the fraction of unique words (rho=-0.15, P0.01).

In women with hot flashes the fraction of unique words declined from approximately one year before first mention of hot flash, reaching a nadir around first mention and returning to baseline after ~1 year, relative to controls. Women with hot flashes who used hormone replacement therapy (HRT) displayed lower rates of unique word usage compared to other users. Though this improved over time, it did not reach control levels even after a year of observation.

Conclusions:

Hot flashes were associated with reduced parameters of cognitive function, specifically unique words, which may reflect recall. Women with hot flashes using HRT, presumably the most symptomatic, displayed the lowest cognitive scores but improved with time, possibly related to treatment effects. We suggest social media as a novel source for cognitive assessment.

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Endocrine gland size is proportional to its target tissue size

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Endocrine glands secrete hormones that travel in the circulation to target tissues where they regulate crucial functions including growth, metabolism and reproduction. The qualitative relationship between hormone-secreting organs and their target tissues is well established, but a quantitative approach that analyzes this relationship through the sizes of tissues is currently limited. This quantitative aspect is important, as it could reveal design principles of endocrine systems, allowing us to study them using engineering concepts of optimality and tradeoffs. In this study, we collected data from the literature on each of 24 human hormones secreted from dedicated endocrine cell types. This includes biochemically different hormones that serve different tissues and physiological functions. We find that the number of cells in an endocrine gland is proportional to the total number of cells in its target tissues, such that a single endocrine cell serves approximately 2000 target cells. This relationship spans 6 orders of magnitude of cell numbers. It suggests an economic principle of cells working near their maximal capacity, and glands that are no bigger than they need to be. Such quantitative relations can help to form a basis for systems endocrinology.

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Challenging Management of a Patient with Hypoparathyroidism

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Permanent hypoparathyroidism is an uncommon complication of total thyroidectomy. Conventional therapy involves calcium and active vitamin D supplementation. However, in some patients a PTH analogue is required, as normocalcemia cannot be achieved without the development of hyperphosphatemia and hypercalciuria. Hypoparathyroidism is a low bone turnover state. PTH replacement therapy converts quiescent bone to high-turnover bone. Thus, the administration of a PTH analogue and its discontinuation can cause rapid shifts in bone turnover and serum calcium level that warrant close monitoring. We describe herein a 52-year-old woman who presented to the emergency room with a high serum calcium level of 18.7 mg/dl, P of 3.5 mg/dl, CTX 807 pg/ml, P1NP 147 ng/ml and acute renal failure. Past medical history includes hypoparathyroidism following hemi thyroidectomy for PTC and completion thyroidectomy. Medical treatment for hypoparathyroidism included teriparatide initiated a year prior to her admission, alfacalcidol 1.5 mcg and calcium carbonate 2000 mg daily. One month prior to admission, teriparatide dose was increased from 20 to 40 mcg daily, while serum calcium prior to dose increment was 8.5-9.5 mg/dl. Two weeks later, the patient started experiencing severe fatigue, polyuria, and polydipsia. Upon admission, teriparatide, calcium, and alfacalcidol were held; the patient received fluids and calcitonin with normalization of serum calcium within 24 hr. When serum calcium reached 9 mg/dl, calcium and alfacalcidol supplementation were gradually renewed. However, the patient developed severe hypocalcemia (6.6 mg/dl) requiring IV calcium administration up to 10 gr/24 hours. Teriparatide 20 mcg daily was renewed 8 days after admission, along with alfacalcidol 2.5 mcg and calcium carbonate 3600 mg daily. Upon discharge serum calcium was 8.8 mg/dl. Two months post-discharge serum calcium increased up to 10.1-10.5 mg/dl and phosphorous increased to 5 mg/dl while alfacalcidol and calcium supplementation doses were gradually reduced to 0.5 mcg and 1200 mg daily, respectively.

Parathyroid hormone replacement therapy in hypoparathyroidism converts low to high turnover bone. Its abrupt discontinuation may cause severe hypocalcemia and significantly higher requirements of active vitamin D and calcium supplementation compared to pre-PTH therapy, reminiscent of hungry bone syndrome. At the end of 2024 PTH1-84 (Natpara) will not be available anymore. Close monitoring after drug discontinuation is required with slow weaning, possibly by using in some patients PTH 1-34 for a limited time.

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Surgery for Papillary Thyroid Carcinoma with Minimal Extra-Thyroid Extension – Is Lobectomy Enough?

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Introduction:

Minimal extra-thyroidal extention (mETE) is often detected after lobectomy for papillary thyroid carcinoma (PTC). While most patients undergo completion thyroidectomy due to this histologic finding, recent studies demonstrated mETE has little impact on the risk of recurrence, questioning the need for further treatment after initial surgery. However, little data is available on the risk of recurrence following lobectomy alone in patients with mETE.

Methods:

A retrospective study was conducted on patients who underwent thyroid lobectomy at a single tertiary care center between January 2012 and December 2020. Only patients with PTC and mETE were included. Data collected included demographics, laboratory, radiologic and cytologic results, surgical and pathological reports. Follow-up data included complications, completion surgeries, diseases free survival, overall survival, and cause of death.

Results:

Sixty-one patients had PTC with minimal extension. Two of those (3.3%) had disease recurrence diagnosed at follow-up. Patients were divided into 22 (36.1%) having extension to the strap muscles, 27 (44.3%) to the perithyroidal fat and 12 (19.7%) having an unknown site of extension. Tumors with posterior microscopic extension had a higher rate of tall cell variant than tumors with anterior microscopic ETE (6, 24% vs 2, 9.1%) and lower rates of positive surgical margins (6, 23.1% vs 9, 42.9%). Tumors with posterior mETE had a trend for higher recurrence with a disease-free survival of 13 months compared to no recurrence in patients with anterior microscopic extension.

Conclusion:

The risk for recurrence in patients undergoing lobectomy for PTC with mETE in our cohort is 3.3%, consistent with low risk of recurrence category. The site of the microscopic extension might be an important, with posterior extension demonstrating a trend of more aggressive tumor variant, higher recurrence rate and a lower disease-free survival compared to tumors with anterior microscopic ETE.

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Efficacy of a single Vitamin D loading dose during hospitalization for hip fracture

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Background:

Vitamin D is a fat-soluble vitamin that regulates calcium and phosphorus homeostasis, Vitamin D is essential for physiological bone mineralization and for optimizing muscle strength and performance. vitamin D deficiency is common in patients with fragility fractures and associated with worse outcome in terms of lower extremity function and risk of recurrent falls.

Vitamin D repletion for post hip fracture patients is important for rehabilitation, fracture prevention and prevention of anti-resorptive therapy side effects.

This study evaluated the efficacy of a single 100,000 IU vitamin D loading dose during hospitalization for hip fractures.

Methods:

According to Wolfson Medical Center protocol, baseline 25-OH-vitamin D level is assessed in post-hip fracture patients and a single loading dose (100,000 IU) is administered. Vitamin D level is re-assessed during hospitalization, 1-5 days after vitamin D loading.

Data was retrospectively extracted from computerized patient files including age, gender, vitamin D levels before and after loading dose. Vitamin D level ≥30 ng/ml was considered sufficient, 20-30 ng/ml insufficient and 20 ng/ml deficient.

Results:

Thirty-two post hip fracture patients were included. The cohort was predominantly female (20/32, 63%); mean age was 80.7 ± 7 years.

Vitamin D deficiency was observed in 23/32 (72%), vitamin D insufficiency in 8/32(25%) and vitamin D sufficiency in 1/32 (3%). Mean baseline vitamin D levels in the study groups were 11.4 ng/dl, 26.25 ng/dl, and 37.9 ng/dl, respectively.

Recurrent vitamin D level assessment was performed 1-5 days after loading dose administration (mean 3.06 days). Mean increment of vitamin D level was 10.94 ng/dl.

Post -loading dose vitamin D levels in the study group were 5/32 (16%) deficient, 17/32 (53%) insufficient, and 10/32 (31%) sufficient.

Discussion:

Vitamin D deficiency and insufficiency are prevalent in post-hip fracture patients. A vitamin D loading dose of 100,000 IU corrected the vitamin D level in the majority, reduced prevalence of vitamin D deficiency from 72% to 16% and increased prevalence of vitamin D sufficiency from 3% to 31%. Loading doses are capable of rapidly increasing plasma vitamin D levels to sufficient, enabling the early provision of osteoporosis therapy post-fracture.

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Familial Resemblance for Body Mass Index at Age 17: A National Intergenerational Cohort Analysis.

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Importance:

Studies on the familial effects of body mass index (BMI) status have yielded a wide range of its heritability.

Objective:

Since genetic and environmental components may vary across the life course, we aimed to assess heritability by measuring fathers, mothers, and their offspring, at the same age.

Design, settings, and participants:

We examined associations between parental and offspring BMI at age 17, as measured at pre-recruitment mandatory medical examination. This cross-generation study included participants examined between 1986 and 2018, whose both parents had their BMI measurement at their pre-recruitment evaluation in the past.

Main Outcome:

We calculated Spearman correlation coefficients between offspring`s BMI and their mothers, fathers, and mid-parental BMI percentile (the average of the mother`s and father`s BMI cohort-and-sex-specific BMI percentile) to estimate heritability. Ordinary logistic regression models were applied to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of obesity compared to normal BMI, according to parental BMI status.

Results:

We identified a total of 447,883 examinees (235,105 males; 212,778 females) with both parents enrolled and measured for BMI at age 17, yielding a total study population of 1,343,649 individuals. Overall, the correlation between mid-parental BMI percentile at age 17 and the offspring`s BMI at age 17 was moderate (rho=0.386). Among females, maternal-offspring BMI correlation (rho=0.329) was somewhat higher than the paternal–offspring BMI correlation (rho=0.266). Among trios where both parents had a normal BMI, the prevalence of overweight/obesity in offspring was 15.4%; this proportion grew to 76.6% when both parents had obesity, and declined to 3.3% when both parents had severe underweight. Compared to normal weight, maternal, paternal, and parental obesity (mid-BMI ≥95th percentile) at age 17 were associated with increased odds of obesity among offspring with adjusted-ORs of 4.96 (95%CI: 4.63-5.32), 4.48 (95%CI: 4.26-4.72), and 6.44 (95%CI: 6.22-6.67), respectively.

Conclusions and Relevance:

The observed correlation between mid-parental and offspring BMI, coupled with a calculated narrow-sense heritability of 39%, underscores the substantive contribution of genetic factors to BMI variation at age 17.

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Patients' perspectives on telemedicine in endocrinology

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Background:

Telemedicine has emerged as an important and sometimes crucial tool in patient care, particularly during the COVID-19 pandemic, offering numerous benefits including time efficiency and improved access to specialized services. However, its adoption in endocrinology remains constrained by the traditional emphasis on the physician-patient relationship and physical examinations, with limited research in this area. Our study aims to evaluate patient's perspectives on telemedicine in outpatient endocrinology clinic.

Methods:

This was a retrospective analysis of surveys delivered via text messages with the assistance of the REDcap application. Surveys were distributed to patients who had telephone appointments, as well as to a control group who had in-person visits from 03/12/22 to 3/12/23.

Objectives:

Assess overall preferences for telemedicine and specific aspects of satisfaction, including communication, waiting times, financial and time burdens. We also wanted to examine variations in preferences levels across different patient groups.

Results:

Of the 850 sent surveys, the response rate was 5% for in-person and 11% for telemedicine visits. In both types of visit surveys, males constituted the majority of patients, accounting for 78.6% in-person and 76.3% in telephone visits, mean age was 63.60+10 (SD) years.

Our findings reveal significant differences between groups in various aspects of satisfaction. Specifically, patients receiving telemedicine treatment reported improved communication compared to those with in-person visits (p 0.001), shorter waiting times (p = 0.033), reduced financial and time burdens (p 0.001), and a general preference for telephone over in-person consultations (p 0.001). However, in-person visits were preferred by both groups mainly for face-to-face interaction (56.6%). Notably, individuals with long-term follow-up and non-diabetic endocrine conditions showed more interest in telemedicine.

Conclusions:

This study demonstrates high satisfaction with telemedicine, but constrained in-person interaction remains a notable limitation. However, it may not suit all patient groups universally or all time-points of patient care, requiring adaptation for broader use. Further research with higher response rate and specifications of different patient population is essential to generalize these findings.

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Evaluation of Serum Glycosylated Hemoglobin for Dysglycemia After Pregnancy Complicated by Gestational Diabetes Mellitus: A National Data Analysis

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Background:

Gestational Diabetes Mellitus (GDM) is a risk factor for future dysglycemia. Currently, it is recommended for individuals with GDM to perform the 2 hours 75-g Oral Glucose Tolerance Test (OGTT), 6-12 weeks after delivery. However, very low compliance with the test leads to underdiagnosis of dysglycemia.

Objective:

To assess the postpartum sensitivity and accuracy of serum HbA1c levels, compared to the 75-g OGTT, for diagnosis of dysglycemia, in a cohort of patients with a history GDM.

Study Design:

We conducted a national - wide retrospective analysis of individuals with a history of GDM and with records of both postpartum 2h-OGTT and serum HbA1c measured at 3-12 months postpartum.

Results:

Between 01 January 2015 until 31 December 2021, A total of 55,119 women were screened, and 9118 were diagnosed with GDM. 677 women had laboratory results of both serum HbA1c levels and 2h 75-gm-OGTT values after delivery. The overall Pearson correlation coefficient between HbA1c and 2h-OGTT was 0.21 (P 0.0001). However, when the 2h-OGTT results were stratified into values ≥ 200 mg/dL, a ROC curve yielded an Area Under the Curve (AUC) of 91.4% [95% CI: 83.9%-98.9%], with HbA1c levels of 5.7% yielding 80.0% sensitivity and 80.8% specificity (95% CI: 44.39-97.48%).

Conclusions:

In selected patients with a recent diagnosis of GDM, serum HbA1c may be used as an auxiliary tool for postpartum diagnosis of dysglycemia. Future studies are needed to determine patient`s compliance with HbA1c testing.

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Completion Thyroidectomy Practice: Can it be Avoided?

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Introduction:

The suggested management of thyroid cancer has been revised in the 2015 American Thyroid Association Management Guidelines, suggesting thyroid lobectomy alone for low-risk thyroid cancer. However, precise patient selection is essential to identify who may need completion thyroidectomy (CT), avoiding the burden of a second surgery. Here, we investigate the role of CT since the new guidelines and the features and causes of CT, aiming to improve pre-operative risk stratification.

Methods:

We perform a retrospective cohort study and a systematic literature review. The original cohort includes patients who underwent CT for thyroid cancer from 2017-2022. Medical records were reviewed for demographics, sonography, cytology, pathology (malignancy type and aggressive features), CT reasons, surgical intervals, and complications. In addition, a systematic literature review was performed and reported according to the PRISMA guidelines, collecting data on CT rates and causes.

Results:

The literature review identified 27 articles with a total sample size of 7,078 hemithyroidectomies. The percentage of CT was 28.8% (weighted mean) with a range of 4.9% to 94.6%. The leading causes for CT surgery were aggressive histologic variants. Among the 54 eligible hemithyroidectomies identified in our center, 37% were CT. The completion cases primarily consisted of female patients (65%), aged 47±13.6 years. The average time between the initial and completion surgeries was 3.75±3.8 months.

Conclusions:

Our findings demonstrate a considerable need for CT. This emphasizes the necessity for improved pre-operative risk stratification methods, such as genetic testing or other clinical scores, and warrants further research to optimize initial surgical decision-making.

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Assessing the Clinical Impact of Molecular Testing in Bethesda V Thyroid Cases

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Background:

The 2023 Bethesda System update firstly incorporated molecular testing as a management option for Bethesda V cytology nodules. Given the notable malignancy risk (74%), the role of molecular testing is controversial. This study aims to evaluate its potential clinical impact.

Methods:

We conducted a retrospective, multicenter study on patients with Bethesda V cytology from 2018-2021 who underwent molecular profiling for thyroid cancer. Data on demographics, sonography, definitive pathology, and genetic variants were analyzed. Genetic variants were categorized per 2015 ATA guidelines.

Results:

Overall, 174 patients were included. Two different molecular tests were used: ThyGeNext and ThyroseqV3, Genetic stratification revealed No-mutation (n=70, 40%), Low-risk (n=54, 31%), and Intermediate-to-High-risk variants (n=49 and 1, 29%). Demographics were consistent across groups. Aggressive pathology features were highest in Intermediate-to-High-risk, followed by low-risk and no-mutation groups (72%, 39.8%, and 30%, P0.001). RAS mutations were the most common among the low-risk group (61.1%), and BRAF V600E predominated in the Intermediate-to-High-risk group (91.8%). Central neck dissections were significantly higher in the Intermediate-to-High-risk group (58% vs. 12.9 and 14.8%, P0.001).

Conclusion:

Our findings suggest that molecular profiling offers a better risk stratification for Bethesda V thyroid lesions and might help determine the extent of surgery. The high rate of mutation-negative nodules highlights the need to choose inclusive and broad genetic tests for these cases.

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Body Mass Index in Late Adolescence and The Risk for Disabling Morbidity in Early Young Adulthood

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Background:

Adolescent obesity is associated with an increased risk of disabling morbidity after the age of 40 years. However, little is known on the risk of developing disabling morbidity before the age of 25 years.

Methods:

This nationwide, population-based, cohort included all Israeli conscripts who underwent a pre-recruitment medical evaluation, during 1998-2017. Body mass index (BMI) at baseline was classified according to US Center for Diseases Control and Prevention percentiles. The primary outcome was the incidence of disabling morbidity that disqualified individuals from completing 2- or 3-year mandatory service. The secondary outcome was the incidence of 104 distinct diseases, categorized into 11 groups according to the International Classification of Diseases 10th Revision. Cox models were applied.

Findings:

A total of 1,095,574 individuals (55.6% men) were included, with 22,680 incident cases of disabling morbidity recorded during 2,484,415 person-years. Incidence gradually increased across BMI groups in both sexes. Among men, compared to those with normal BMI, the adjusted HRs were 0.89 (0.84-0.95), 1.22 (1.17–1.28), 1.40 (1.33-1.49), 2.89 (2.66-3.14), and 5.32 (4.51-6.26), for the underweight, overweight, obese I, obese II, and obesity III subgroups, respectively. Among women, the respective adjusted HRs were 0.98 (0.86-1.12), 1.27 (1.18-1.37), 1.64 (1.46-1.84), 4.14 (3.58-4.78, and 7.52 (5.79-9.75). Results persisted in sensitivity analyses restricted to individuals stationed in non-combative office employments, which are equivalent to the civilian setting.

Interpretation:

Obesity was associated with an increased risk of disabling morbidity before the age of 25 years in otherwise healthy adolescents.

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The association between elevated TSH levels and prolonged length of stay among adult diabetic patients hospitalized in internal medicine departments: A large historical cohort study

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Background:

Diabetes mellitus (DM) and hypothyroidism are two of the most common endocrine disorders in clinical practice. The association between increased TSH levels and poor hospital outcomes among patients with DM was studied previously in small populations. This study aimed to evaluate the association between elevated TSH levels and prolonged length of stay (LOS) among a large population of patients with DM hospitalized in internal medicine departments.

Methods:

A historical cohort study of all adult patients (aged 18+ years) with DM admitted to a large medical center between 2014-2022 and hospitalized in internal medicine departments was performed. Data on patients` characteristics, hospital stay, and in-hospital mortality were collected. Elevated TSH level was defined as TSH4.7μIU/mL. Prolonged LOS was defined as LOS above the 75th percentile or in-hospital mortality. Univariate and multivariable analyses were applied and propensity score matching was also used to control for differences between patients with normal and elevated TSH Levels.

Results:

A total of 19,066 patients were included in this cohort (median age 75.6 years, IQR 75.9-83.3), among whom 1,524 (7.9%) had elevated TSH levels. Prolonged LOS was more common among patients with elevated TSH levels (before matching: 38.6% vs. 29.1%, p0.001; after matching: 38.7% vs. 32.6%, p=0.001). After adjustment for potential confounders elevated TSH levels were independently associated with prolonged LOS (odds ratio=1.223 95% CI 1.074-1.394, p=0.002).

Conclusion:

Elevated TSH levels in diabetic patients hospitalized in internal medicine departments are associated with prolonged hospital stays. This finding emphasizes the importance of hypothyroidism evaluation among diabetic patients.

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Characterization of beta cell senescence during aging and in diabetes

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A growing body of evidence supports the involvement of beta cell senescence as a potential pathological cellular state linked to islet inflammation and dysfunction in diabetes. Therefore, the removal of senescent beta cells through senolysis is proposed as a promising therapeutic strategy for both Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). However, a comprehensive characterization of human senescence-like beta cells is lacking and the relationship between age-related naturally accumulating senescence-like beta cells and those associated with the diabetic state remains unestablished. To characterize senescence-like beta cells we compared the expression profile of beta cells expressing the senescence master regulator p16 (CDKN2A positive, senescence-like) to CDKN2A negative beta cells from scRNAseq data of islets obtained from both non-diabetic (ND) T1D and T2D donors and examined their distinctive response to metabolic and inflammatory stress. We reveal that senescence-like beta cells which naturally accumulate with age exhibit a more mature signature accompanied by a cell cycle arrest and stress-related signatures; however, they do not display SASP (Senescence-Associated Secretory Phenotype). In donors with T2D, an increased proportion of these cells is coupled with heightened senescence-related characteristics and signs of compromised health, such as the loss of maturation markers and impaired exocytosis, suggesting that beta cells from T2D donors undergo a “stress-induced senescence”. Notably, in donors with T1D, a reduced proportion of senescence-like beta cells implies an elimination process, as the remaining senescence-like beta cells show an upregulation of interferon response genes. This upregulation can potentially intensify the immune system`s response, making the senescent beta cells more susceptible to T-cell-mediated destruction. This observation supports the notion that in T1D, senescence-like beta cells serve as hubs for inflammatory response. Finally, exposing non-diabetic (ND) human islets to various stressors initiated "stress-induced senescence" preferentially in senescence-like beta cells and induced the secretion of SASP. Altogether, our findings suggest that senescence-like beta cells, being predisposed to diabetic-related stress conditions, possess a greater potential to contribute negatively to the pathology of both T1D and T2D.

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G6PC2 controls glucagon secretion by defining the setpoint for glucose in pancreatic alpha-cells

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Impaired glucose suppression of glucagon secretion (GSGS) is a hallmark of type 2 diabetes. Given that hyperglucagonemia can exacerbate elevated blood glucose levels, and its correction could provide a therapeutic benefit, there has been a growing interest in elucidating the precise mechanisms governing glucagon release by alpha-cells. A critical role for alpha-cell-glucose sensing mechanism has been established through manipulations of the glycolytic enzyme glucokinase (GCK) which changed the setpoint for glucose-suppression of glucagon secretion (GSGS). The catalytic subunit of the islet-specific glucose-6-phosphatase enzyme (G6PC2) opposes the action of glucokinase and creates a futile substrate cycle. Multiple GWAS studies have linked polymorphisms in G6PC2 with variations in fasting blood glucose and HbA1c levels and suggested a functional impact of these SNPs on G6PC2 expression in beta-cells. As G6PC2 is expressed in alpha cells as well, we hypothesized that reduced G6PC2 levels would suppress glucagon secretion from α-cells in response to glucose. Analyzing scATACseq and bulk RNAseq data from human alpha cells, we reveal that two trait-associated SNPs located within alpha cell open chromatin regions are linked to altered G6PC2 transcript levels. This finding supports a functional role for G6PC2 in controlling glucose sensing within alpha cells. To examine the role of G6PC2 in alpha-cell function we created an alpha-cell specific gene ablation of G6PC2 (alpha-G6PC2-KO). These mice exhibited a decrease in fasting blood glucose and glucose-suppressed glucagon levels. No change was detected in insulin levels, islet hormone content, or islet morphology. Our *ex-vivo* glucose uptake study showed increased retention of 2-deoxyglucose in islets from alpha-G6PC2KO providing further evidence for a physiologic role of G6PC2 in alpha-cells. Finally, we confirmed the relevance of our findings to human islets by downregulating G6PC2 in alpha-cells with lentivirus expressing shRNA-against G6PC2 and measuring GSGS in alpha-only pseudo-islets, which demonstrated enhanced glucose inhibition of glucagon secretion. Our findings provide evidence that in alpha cells, G6PC2 affects glucagon secretion by modulating the set point for glucose sensing and GSGS and suggest that G6PC2 inhibitors could play an important role in the treatment of patients with Type 2 diabetes, as G6PC2 specific inhibitors are expected to increase glycolytic flux in both beta and alpha-cells and thus affect islet hormones in a bidirectional fashion, increasing insulin and lowering glucagon secretion without affecting hepatocyte glucose flux and thus avoiding untoward affects associated with glucokinase activators.

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Impaired glucose homeostasis in the short-telomere Telomouse

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Type 2 diabetes (T2D), marked by persistent hyperglycemia, is a common chronic metabolic disease with a prevalence exceeding 20% in individuals aged 65 and above. It stems from pancreatic β-cell failure to meet the increased insulin demand due to peripheral insulin resistance. Despite being a key risk factor, the molecular mechanisms linking aging to T2D remain unclear. Telomere shortening or damage, one of the main hallmarks of aging, can trigger cellular senescence, an increasingly recognized regulator of age-related metabolic disorders through the induction of inflammation and insulin resistance. Therefore, we hypothesize that telomere attrition plays a central role in accelerating the development of T2D with age. However, establishing telomere biology as a causative factor in T2D has been challenging thus far, due to model limitations. Here we utilized the Telomouse model, which has human-length telomeres, to assess parameters of prediabetes, both in the natural aging process and under diabetic conditions induced by a high-fat, high-sucrose diet (HFHS). We show that Telomice exhibit age-related insulin resistance, increased fasting blood glucose and glucose intolerance, which are characteristic hallmarks of the pre-diabetes stage. Furthermore, these parameters worsen in later generations of Telomice, correlating with telomere shortening in successive generations. Under HFHS challenge, these metabolic parameters worsen, along with decreased glucose-stimulated insulin secretion, suggesting the involvement of pancreatic β-cell dysfunction. These data confirm that Telomouse emerges as an invaluable tool for exploring the role of telomere biology in age-related metabolic decline.

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A Case Report of Gigantism and AIP Gene Mutation: Implications for Genetic Counseling and Preimplantation Genetic Diagnosis

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This medical case report presents the case of a patient who experienced accelerated growth, facial changes, and enlargement of hands and feet since the age of 17. Despite having a sister suffering from acromegaly, the patient did not undergo endocrine evaluation until the age of 25 when he was diagnosed with gigantism. Magnetic resonance imaging (MRI) revealed the presence of a macroadenoma with suprasellar extension reaching the optic chiasm. The patient underwent transsphenoidal surgery and excision of a sparsely granulated somatotroph adenoma that was Pit1 positive and exhibited weak immunostaining for growth hormone (GH). Insulin-like growth factor 1 (IGF1) levels normalized after surgery, and a fasting GH level was 0.6 ng/mL.

Given the family history and the early onset of the disease, genetic counseling was recommended. Genetic testing revealed a heterozygote mutation in the AIP gene (c713G-A). This finding prompted the recommendation for genetic testing of all first-degree relatives. The patient and his wife, who desired to have children, were referred to obstetrics and gynecology for pregestational diagnosis. Family segregation testing indicated that the patient`s mother also carried the same AIP mutation.

Preimplantation genetic diagnosis (PGD) was conducted, revealing that 11 out of 20 embryos were carriers of the AIP mutation. The non-carrier embryos were selected for implantation, and pregnancy was achieved. Efforts to inform first-degree relatives about the importance of genetic testing were undertaken, and one sister was tested and found to be healthy. Other siblings have not yet been tested. The patient`s mother, identified as an AIP carrier, underwent endocrine laboratory tests that showed GH, IGF1, and prolactin levels within the normal range. Brain MRI did not reveal a pituitary lesion.

This case highlights the significance of genetic counseling and testing in patients with familial endocrine disorders, the potential implications of AIP gene mutations, and the challenges faced in reproductive decision-making for affected individuals and their families.

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Mechanisms of Aldolase B mediated beta cell glucotoxicity

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Background:

Diabetes is associated with beta-cell dysfunction attributed in part to the toxic effects of elevated glucose levels (glucotoxicity). Initially, hyperglycemia is mitogenic, driving beta-cell replication, however, chronic hyperglycemia leads to dysfunction and failure of productive beta-cell proliferation. The glycolytic enzyme most upregulated in human and rodent beta-cells exposed to high glucose is Aldolase B (AldoB), a key player in glucose and fructose metabolism in the liver, but usually not highly expressed in beta-cells. Although numerous studies discuss possible mechanisms through which AldoB could affect beta-cells, none has shown causality.

Methodology and findings:

To explore the hypothesis that AldoB mediates glucotoxic effects on beta cells we first determined the expression profile of AldoB positive beta-cells obtained from single cell transcriptome of diabetic mice and revealed upregulation of pentose phosphate pathway (PPP) genes and the polyol pathway which regulates lipid metabolism, while respiration genes were downregulated. GSIS on INS1 overexpressing AldoB was not altered whereas, mitochondrial respiration efficiency, tested using the Seahorse XFe96 analyzer, revealed decreased ATP production at 35mM but not 20mM glucose. To determine whether AldoB overexpression inhibits beta cell regeneration we measured the proportion of ki67 positive beta cells in islets isolated from AldoB ablated (AldoBKO) mice and control littermates previously exposed to extreme glucose concentration. This FACS analysis demonstrated increased proportion of Ki67 positive beta cells in AldoBKO islets expose to 35mM glucose. Based on previous studies, we investigated the hypothesis that AldoB exerts its negative affect through inhibition of AKT signaling. We performed immunoblot assays to quantify phosphorylated AKT in islets isolated and treated with high glucose. We found increased abundance of p-AKT in AldoBKO islets, supporting a role for AldoB in inhibiting AKT signaling in beta cells under extreme hyperglycemic conditions.

Conclusions:

Our findings support the hypothesis that aberrant levels of AldoB in beta cells exerts its negative effect through dysregulating the balance between oxidative metabolism and glycolysis and demonstrate a role for AldoB in suppressing mitochondrial respiration efficiency under extreme glucose concentrations and in inhibiting regeneration potential. Furthermore, our findings suggest a non-enzymatic function for AldoB in inhibition of the AKT signaling as suggested by previous studies. The results of this study provides evidence addressing the question of whether AldoB function is an attractive target for the development of novel therapeutics for the prevention and treatment of diabetes.

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Extensive elimination of acinar cells during normal postnatal pancreas growth.

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While programmed cell death plays important roles during morphogenetic stages of development, post-differentiation organ growth is considered an efficient process whereby cell proliferation increases cell number. We demonstrate that early postnatal growth of the pancreas unexpectedly involves massive acinar cell elimination. Measurements of cell proliferation and death in the human pancreas in comparison to the actual increase in cell number predict daily elimination of 0.7% of cells, offsetting 88% of cell formation over the first year of life. Using mouse models, we show that death is associated with mitosis, through a failure of dividing cells to generate two viable daughters. In p53-deficient mice, acinar cell death and proliferation are reduced,
while organ size is normal, suggesting that p53-dependent developmental apoptosis triggers compensatory proliferation. We propose that excess cell turnover during growth of the pancreas, and presumably other organs, facilitates robustness to perturbations and supports maintenance of tissue architecture.

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Disrupted RNA editing in beta cells mimics early-stage type 1 diabetes

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Genetic and experimental studies support a role for an anti-viral type I interferon (IFN-I) response to double-stranded RNA (dsRNA) in the early stages of Type I diabetes (T1D). However, a viral etiology has not been established, raising the possibility that the interferon response results from an endogenous source of dsRNA. Indeed, a recent genetic study implicated reduced editing levels of double-stranded RNA (dsRNA) in the development of autoimmune diseases, including T1D. Thus, we hypothesized that defects in RNA editing in pancreatic islet cells may cause the accumulation of endogenous dsRNA and initiate islet inflammation, a hallmark of early-stage T1D.

We have generated a mouse model for deficient RNA editing, using knockout of the RNA editing gene Adar in pancreatic beta and alpha-cells. We have used fluorescent immunostaining of pancreatic sections and standard functional assays on isolated islets to characterize islet inflammation and beta-cell phenotype following Adar disruption. To elucidate the molecular basis for islet inflammation in mutant mice, we have performed bulk RNA-sequencing on FACS-sorted beta-cells.

Defective RNA editing in mouse beta-cells strikingly recapitulates key features of early T1D: a strong interferon response triggered by dsRNA, causing massive insulitis; disrupted expression programs in beta-cells culminating in beta-cell death and diabetes, while alpha-cells remain unaffected. Furthermore, we discovered that the interferon response in both mutant and wild-type beta-cells depends on cellular metabolic activity, specifically through calcium signaling. We further show that enforced hyperglycemia in Adar-mutant mice enhanced the inflammatory phenotype.

Our findings indicate that deficient editing of dsRNA in islets leads to heterogenous islet inflammation and destruction, resembling features of early-stage T1D. Our results also support a potential vicious cycle whereby metabolic stress in damaged islets enhances beta-cell workload, further boosting the interferon response, islet inflammation and beta-cell dysfunction towards diabetes.

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A combination of computational and experimental tools reveals novel mechanisms regulating MKRN3, and its function in GnRH-secreting mouse neurons

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Introduction:

Central precocious puberty (CPP) is sometimes associated with loss-of-function mutations in Makorin-Ring-Finger-Protein 3(MKRN3). Moreover, hypothalamic-MKRN3 mRNA levels decrease before puberty, suggesting its repressive role on GnRH, and the inhibition of puberty onset. Although this decrease is well established, the mechanisms that mediate MKRN3-downregulation and the function of MKRN3 in hypothalamic GnRH neurons are unclear.

Aims:

We aim to elucidate the mechanisms that regulate MKRN3-expression in GnRH neurons, and its role in these cells.

Methods:

To find genes whose expression correlates with that of Mkrn3, we analysed RNA datasets from brain samples of rats and mice, and rat-mediobasal-hypothalami(MBH), through the juvenile to adulthood transition. This might indicate factors that control Mkrn3 expression, as well as commonly-regulated factors and downstream targets. We then utilized hypothalamic GnRH-neuronal cells (GT17), to identify and characterize factors that regulate Mkrn3. We over-expressed GFP-Mkrn3 in these cells and performed RNA-sequencing and mass-spectrometry (MS/MS) analyses to determine effects on the expression of other genes and proteins. We also performed immunoprecipitation via the GFP-tag, to identify RNAs (via RIP-seq) and proteins (via AP-MS/MS) that interact with Mkrn3.

Results:

The bioinformatic screen identified ~300 differentially-expressed genes, whose expression correlated with that of Mkrn3. These included Activin-receptor-type1C (Acvr1c) whose expression is negatively correlated with that of Mkrn3 during development. To test whether Acvr1c represses Mkrn3, we expressed a constitutively-active Acvr1c in GT1-7 cells, which led to a reduction in Mkrn3 mRNA levels. Furthermore, induction of the endogenous-Acvr1c by activin A or activin B, reduced Mkrn3-expression. Acvr1c signals through the transcription factors SMAD2/3. We show that Smad2/3 bind the Mkrn3 promoter in GT1-7 cells, and that knockdown of SMAD2 increases Mkrn3 expression. The MS/MS and RNA-seq identified ~500 proteins and ~600 genes whose levels change after over-expression of Mkrn3. The AP-MS/MS and RIP-seq analyses revealed hundreds of protein and RNA interactors of Mkrn3, including those involved in RNA binding and regulating translation.

Conclusions:

We have identified several potential regulators of MKRN3 in GnRH-neurons, including the Acvr1c-mediated pathway, that might downregulate Mkrn3 expression during development to allow puberty onset. Such a role for this pathway is supported by reports that Acvr1c-KO in mice causes a delay in puberty. The combination of MS/MS and RNA-seq analyses indicate populations of genes and proteins with changes only in their RNA-expression, only in their protein-expression, or in both. AP-MS/MS and RIP-seq after pull-down of the GFP-tagged Mkrn3 has revealed novel protein and RNA interactors of Mkrn3.

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Single-cell and experimental analyses indicate pathways of transcription factor-driven differentiation of post-natal pituitary stem cell to gonadotropes

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The anterior pituitary gland is composed of various cell-types which synthesize and secrete the regulatory trophic hormones. In addition, pituitary stem cells (PSCs) reside within the gland, enabling its growth and adaptation to physiological demands through their differentiation. Although PSCs are capable of differentiating to all of the hormone-producing cell-types, during the neonatal period, they differentiate mainly to gonadotropes. The signals that direct PSCs differentiation specifically along the gonadotrope lineage, and the mechanisms involved in this process are unknown. We hypothesized that the differentiation is driven by expression of a series of specific transcription factors (TFs), each binding to regulatory regions in the genome, which leads to the activation of a particular subset of target genes. To investigate this, we utilized single-cell RNA sequencing data of PSC-derived cells from neonatal mice. These pituitary cells are in various stages along the differentiation process: from PSCs, through pre-gonadotropes which begin to express gonadotrope markers such as *Cga*, *Foxl2* and *Nr5a1*, and reaching mature gonadotrope cells. The combination of regulon analysis by the SCENIC package, with psuedotime analysis by the Slingshot package, indicated several putative regulators of this postnatal gonadotrope differentiation. These included the basic helix-loop-helix (bHLH) pioneer TF, NeuroD1, which is known to play roles in neurogenesis and pancreas development. Its regulon in the postnatal pituitary is primarily active in differentiating gonadotropes, and its downstream putative targets include the gonadotrope-specific markers *Nr5a1* and *Gnrhr*. The fact that NeuroD1 expression precedes that of these putative targets, suggests a possible regulatory effect. Additional putative targets of NeuroD1 are the neuronal bHLH TFs Nhlh1/2, whose expression is also specific to the gonadotrope lineage, and are predicted to activate *Nr5a1*. Experiments performed in gonadotrope-progenitor cell lines further support these predictions. Firstly, NeuroD1 overexpression induced the expression of *Nr5a1*, *Nhlh1* and *Nhlh2*. Chromatin-immunoprecipitation (ChIP) showed that NeuroD1 binds to the gonadotrope-specific regulatory elements of these genes, indicating a direct regulatory effect. Nhlh1 and Nhlh2 also appear to bind a distal enhancer of *Nr5a1*. These findings uncover a novel role for NeuroD1, Nhlh1 and Nhlh2 in gonadotrope differentiation, and expand our understanding of the TF-driven pathways and underlying molecular mechanisms involved in the passage of pituitary stem cells to become gonadotropes in the neonate.

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A distal super-enhancer of the *Fshb* gene coordinates activity of the locus and shapes the chromatin landscape in a mouse model of menopause

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Circulating levels of follicle stimulating hormone (FSH) increase dramatically at the time of menopause, and recent reports have suggested that this contributes to age-related disease. We hypothesized that the *Fshb* gene undergoes epigenetic modification during the menopause transition, which mediates some of the increase in its expression. This study focuses on the role of a putative super-enhancer (SE) in the large ~230 kbp "gene desert" which separates *Fshb* from its neighboring *Kcna4*. The region includes several sites of open chromatin and enhancer-specific histone modifications, seemingly containing three separate enhancer elements. We show, using chromatin conformation capture (3C) and UMI-4C, that these loci are in physical contact with the proximal promoters of both *Fshb* and *Kcna4* genes. RNA-seq analysis revealed that the region is transcribed abundantly to chromatin-associated lncRNAs. Levels of these lncRNAs, as well as *Fshb* and *Kcna4* mRNAs, increased following ovariectomy which serves as a mouse model for menopause, suggesting possible enhancer activity directed at both genes. Ovariectomy reduces the repressive effects of inhibin on stimulation by activin, so we hypothesized that activin might drive this increased enhancer activity. Indeed, activin treatment of gonadotrope cells significantly elevated levels of the lncRNAs, as well as *Fshb* and *Kcna4* mRNAs. We found, using chromatin immunoprecipitation (ChIP), that binding of BRD4 and MED1, two transcriptional coactivators which mark SEs, increased dramatically after activin treatment, as did binding of the CTCF insulator protein. Two of the enhancer regions were also seen to bind the transcription factor FOXL2 which is essential for gonadotrope function and fertility. Using gonadotrope cell lines that stably express dCas9-KRAB and various gRNAs, we targeted KRAB to each of these regions. Differential effects on *Fshb* and/or *Kcna4* mRNA levels were evident when targeting the distinct sites, most notably in the *Fshb* response to activin which could be completely abolished. Our results indicate that this SE can activate expression of both *Fshb* and *Kcna4* in response to activin, and individual elements preferentially target one, or both, of the genes. *Kcna4* encodes a potassium-voltage gated channel whose role in gonadotrope biology is not known, but could perhaps play a role in hormonal release, explaining its sometimes-coordinated expression. Our work sheds new light on the epigenetic regulation of *Fshb* and its increase at menopause, and highlights a role for a distal SE which can be employed to regulate *Fshb* and/or its neighboring gene.

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Changes in DNA methylation patterns linearly associated with DHEAS levels in prepubertal children are found near puberty-related genes

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The adrenal glands start synthesizing the androgens dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as early as 3 years of age. Their production continues to increase, and they can be detected in the blood at around age 6 years. Previous studies showed that high levels of these androgens prior to puberty correlate with earlier puberty onset. We hypothesized that some of this effect might be due to stable changes in DNA methylation, affecting expression of genes involved in pubertal development. We analyzed the correlation between DHEAS levels and pubertal measurements in children of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. We found that boys and girls who had higher pre-pubertal DHEAS levels, had more advanced pubic hair growth; girls also had more advanced breast development, earlier menarche and longer menstrual cycles later in life. We investigated the linear regression between changes in individual and regional methylation, and the levels of DHEAS in the same population of prepubertal children. Annotated genes near the most significantly correlated individual CpGs, included those whose methylation or expression levels were previously shown to be associated with puberty onset (i.e. MEGF11, FAM115B, PTPRN) or sex steroid levels (i.e. SORCS2, PRRT1). We also used a regional approach, to assess linear regression at CpG islands with the DHEAS levels. The genes annotated near the significant islands were intersected with a previously generated set of puberty-related genes. We found 9 genes in girls (LHCGR, FGFR1, IGF2, SOX9, MAPK3, STAT3, CALCA, FTO, SRD5A2) and 14 in boys (ESR2, AKT1, FGFR1, NR5A1, FTO, PPARA, MMP9, SRC, DNMT3A, KLHL34, ZNF775, CREB1, C3ORF38, GDNF) to meet our criteria. This suggests that expression of these puberty-related genes might be regulated by DHEAS-dependent methylation changes. LHCGR expression increases in the ovaries at the time of prepubertal adrenarche in our new animal model, the spiny mouse, despite no change in LH or FSH gene expression in the pituitary. Furthermore, hypomethylation of the LHCGR promoter has been shown to be prevalent in women with polycystic ovarian syndrome (PCOS), and in DHEA-induced PCOS mice. These findings suggest that an increase in LHCGR expression levels might be an early driver of puberty which is regulated by DHEAS, and in exaggerated levels this could promote PCOS development. Further research of the genes uncovered in this research can reveal mechanisms by which pre-pubertal adrenal DHEAS promotes puberty onset and clarify the relationship between these two major developmental milestones.

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The role of suprachiasmatic VIP neurons in circadian rhythm regulation of the estrous cycle in female mice

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Jet lag and shift work disrupt the menstrual cycle and decrease fertility. The circadian pacemaker, the suprachiasmatic nucleus (SCN), is known to modulate ovulation. It was previously suggested that the suprachiasmatic vasoactive intestinal peptide (VIP) neurons (SCN^{VIP}) are directly connected to gonadotropin-releasing hormone (GnRH) neurons, which control the release of reproductive hormones. However, their dynamics and circuitry to GnRH neurons are poorly understood. To further understand this connectivity, we recorded bulk GCaMP6s signals from SCN^{VIP} neurons *in vivo* in mice over days. A machine learning classifier could distinguish between estrous cycle days, specifically in the late afternoon. Next, we tested how these afternoon activity patterns related to light information, as SCN^{VIP} neurons exhibit immediate responses to light via the retinohypothalamic track. Under regular light conditions, female mice ovulate every 4-5 days, whereas, under near-complete dark conditions, ovulation was reduced to every 7-8 days. Based on our recording session, we estimated that light in the late afternoon could rescue this reduction. Indeed, the afternoon light was able to rescue the estrous cycle frequency reduction completely. Specific activation of SCN^{VIP} neurons with chemogenetics rescued this reduction, suggesting the unique role of SCN^{VIP} neurons in the light perception control of GnRH neurons. To strengthen this point, we used gene editing to downregulate VIP receptors on GnRH neurons. This caused a reduction in the estrous cycle regulation, and the late afternoon light rescue was absent. Together, these experiments suggest that the time-of-day-dependent activity of SCN^{VIP} neurons is essential for estrous cycle regularity, connecting light information directly to GnRH neurons as a necessary permissive signal in the late afternoon.