האגודה הישראלית לאנדוקרינולוגיה
Israel Endocrine Society

הכנס המדעי ה-51
של האגודה הישראלית לאנדוקרינולוגיה

22-23 במאי 2023

מלון דיויד אינטרקונטיננטל, תל אביב

PROGRAM BOOK

שלום חברים,

ברוכים הבאים לאתר הכנס המדעי ה 51 של האגודה הישראלית לאנדוקרינולוגיה!

הכנס יתקיים ב 23-22 למאי במלון דיויד אינטרקונטיננטל בתל אביב.

הכנס השנתי נותן לנו הזדמנות לבחון מזוויות שונות את דרכי החשיבה שלנו ולהעשיר את הידע בתחומים שונים מתוך השדה הקליני והבסיסי באנדוקרינולוגיה.

הכנס מאפשר ללמוד על שיטות מחקר חדשות ועל כלי טיפול חדישים. בעיקר, הכנס נותן במה לעוסקים בתחום להציג את עבודתם, לקבל משוב וליצור שיתופי פעולה שבסופו של דבר מעשירים את כולנו. נשמח אם תעודדו רופאים צעירים, חוקרים צעירים וסטודנטים לקחת חלק פעיל בכנס.

הכנס גם מאפשר לנו להוקיר את העושים במלאכה, אתם מוזמנים לקרוא על פרסי האגודה ולהציע מועמדים לפרסים השונים.

הצטרפו אלינו, ליומיים של הרצאות, סדנאות ותערוכה המשלבים מפגש חברתי-מקצועי שלמדנו כל כך להעריך.

פרופ' גיל ליבוביץ

נשיא האגודה הישראלית לאנדוקרינולוגיה

ד"ר יעל קופרמן

יו"ר הכנס השנתי

ד"ר מרב פרנקל

מזכירת האגודה הישראלית לאנדוקרינולוגיה

חסויות

Platinum

AstraZeneca

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Silver

MEDISON

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Pfizer

GEFFEN MEDICAL גפן מדיקל

Medtronic Further, Together

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 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 בחקר הפוריות ושינה את שמה ל: "חקר הורמונים."

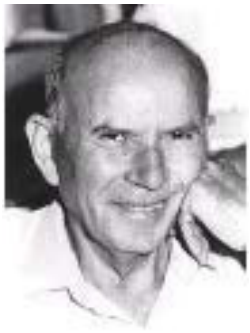
בזכות תכונותיו התרומיות כאינטלקטואל וכמדען, נשא פרופ' לינדנר תפקידים רבים נוספים: הוא מונה במכון ויצמן כדיקן הפקולטה לביולוגיה, לראשות הועדה לקידום מדענים ולוועדה המייעצת של נשיא המכון. בנוסף לכך, הוא היה חבר בחבר הנאמנים של ביה"ח הדסה בירושלים, היה פעיל בהקמת הפקולטה לווטרינריה ואף היה נשיא האגודה הישראלית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

בתקופת כהונתו החלה מסורת קיום הכנסים השנתיים. פרופ' לינדר היה פעיל גם בארגונים בינל"א: חברת בועדות WHO של מכון מקס פלאנק בגרמניה, של INSERM בצרפת, של ארגונים אנדוקריניים בינל"א וב- Editorial 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 לאנדוקרינולגיה. 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

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 איזור 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 הנוירואנדוקרינולוגיה 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 הגונדוטרופיניפ 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 בויסות חום הגוף ובתפקיד מערכת העצבים המרכזית בויסות 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 הנוירואנדוקרינולוגיה. 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 לאוכלוסיה 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.

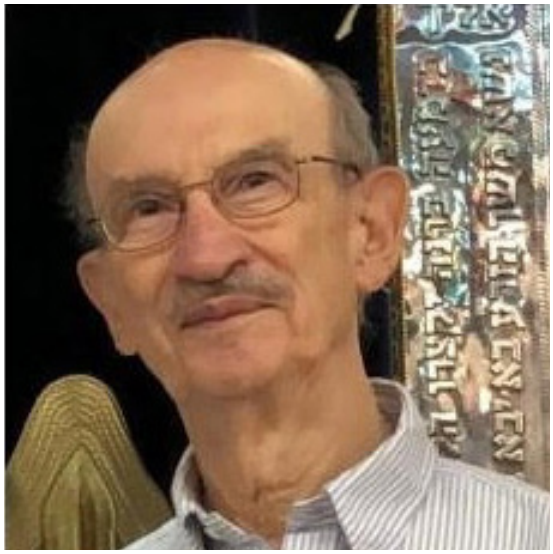
ביוזמתו עבר ביה"ח שינויים ניכרים לקראת הפיכתו לבית-חולים מודרני ואוניברסיטאי. במסגרת שיקום המחלקה, הקדיש פרופ' חוברס תשומת לב רבה לשטח האנדוקרינולוגיה ובמיוחד לנושא הסוכרת. הוא הקים יחידת סוכרת עם ציוד מודרני וייחודי להדרכה, אבחון, טיפול ומחקר קליני. במקביל לעבודתו בביה"ח ביקור חולים, מונה פרופ' חוברס 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 מותיקי האגודה הישראלית לאנדוקרינולוגיה, נפטר באופן פתאומי ב -3.2.89 , לאחר מותו, יסדה משפחתו פרס לזכרו לשם קידום המחקר האנדוקריני בישראל. הפרס מוענק לחוקר צעיר, מתחת לגיל 54 עבור עבודה בתחום האנדוקרינולוגיה שפורסמה בשנה האחרונה (או עומדת להתפרסם).

זוכי פרס חוברס:

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

פרופ' אורי אהרון ליברמן ז"ל – מילים לזכרו



פרופ' אורי אהרון ליברמן 1935-2022

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.

זוכת פרס ליברמן:

2023 - ד"ר איריס ורד

SCIENTIFIC PROGRAM

Monday, May 22, 2023

08:00-09:00 **Registration, Refreshments & Exhibition**

09:00-10:30 **Parallel Session:**
Abstracts: Diabetes, obesity, and metabolism 1 **Hall A**
Chair: Dr. Irit Hochberg, Rambam Medical Center
Dr. Moran Rathaus, Sheba Medical Center

09:00-09:12 **Mapping the Metabolic Reprogramming Induced by Sodium-glucose Cotransporter 2 Inhibition**
Aviram Kogot-Levin[1], Yael Riahi[1], Ofri Mosenzon[1], Ifat Abramovich[2], Bella Agranovich[2], Liat Kadosh[1], Rachel Ben-Haroush Schyr[3], Doron Kleiman[3], Erol Cerasi1, Liad Hinden4, Danny Ben-Zvi[3], Joseph Tam[4], Eyal Gottlieb[2], Gil Leibowitz[1]
[1]*Diabetes Unit and Endocrine Service, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
[2]*The laboratory for Metabolism in Health and Disease, Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*
[3]*Department of Developmental Biology and Cancer Research, Institute of Medical Research Israel-Canada, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel*
[4]*Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*

09:12-09:24 **Obesity in patients with youth-onset T2D: the Israeli cohort**
Nehama Zuckerman-Levin[1,2], Meidan Cohen[1,2], Moshe Phillip[3,4], Ariel Tenenbaum[3,4], Ilana Koren[2,5], Yardena Tenenbaum-Rakover[2,6], Osnat Admoni[6], Eli Hershkovitz[7,8], Alon Haim[7,8], Kineret Mazor Aronovitch[4,9,10], David Zangen[11,12], David Strich[12,13], Avivit Brener[4,14], Yonatan Yeshayahu[8,15], Yossi Schon[16], Marianna Rachmiel[4,16], Tal Ben-Ari[4,17], Floris Levy-Khademi[12,18], Afif Nakhleh[1,2], Rami Tibi[1,2], Ram Weiss[1,2], Yael Lebenthal[4,14], Orit Pinhas-Hamiel[4,9,10], Naim Shehadeh[1,2,19]
[1]*Pediatric Diabetes Clinic, Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus, Haifa, Israel*
[2]*The Ruth & Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*
[3]*The Jesse Z and Sara Lea Shafer Institute of Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*
[4]*Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel*
[5]*Pediatric Endocrine and Diabetes Unit, Carmel Medical Center, Haifa, Israel*
[6]*Pediatric Endocrine Institute, Ha'Emek Medical Center, Afula, Israel*
[7]*Pediatric Endocrinology and Diabetes Unit, Soroka Medical Center, Beer Sheva, Israel*
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[15]*Pediatric Endocrine Unit, Department of Pediatrics, Assuta Ashdod Medical Center, Ashdod, Israel*
[16]*Pediatric Endocrinology Institute, Shamir Medical Center (Assaf Harofeh), Zerifin, Israel*
[17]*Pediatric Endocrinology and Diabetes Unit, Edith Wolfson Medical Center, Holon, Israel*
[18]*Pediatric Endocrinology and Diabetes Unit, Shaare Zedek Medical Center, Jerusalem, Israel*
[19]*The Azrieli Faculty of Medicine, Bar- Ilan University, Safed, Israel*

09:24-09:36 **The cytokine SDF-1 and its receptors regulate liver metabolism – a fresh look on intrahepatic communication**
Kfir Sharabi[1]
Institute of Biochemistry, Food Science, and Nutrition, The Hebrew University of Jerusalem, Rehovot, Israel

09:36-09:48 **Gut microbiota and physical capacity in older people with diabetes**
Naama Peltz-Sinvani[1], Michal Azmon[1,2], Tal Yahalom Peri[1], Yamit Bason[1], Tali Cukierman-Yaffe[1,3]
[1]*The Center for Successful Aging with Diabetes, Endocrinology Institute, Chaim Sheba Medical Center, Ramat-Gan, Israel*
[2]*The Physiotherapy Department, Faculty of Health Sciences, Ariel University, Ariel, Israel*
[3]*The Epidemiology Department, Sackler School of Medicine, Herczeg institute of aging, Tel-Aviv University, Tel-Aviv, Israel*

09:48-10:00 **Diabetologist Training Program for Family Physicians in Israel: 2017-2022**
Irit Hochberg[1,2], Ronit Kalmanovich Dickstein[3], Liat Barzilay Yoseph[2,4], Idit F. Liberty[5,6], Riad Taher[1,2,7], Ofri Mosenzon[8,9]
[1]*Institute of Endocrinology, Diabetes and Metabolism, Haifa, Rambam Health Care Campus,, Haifa,, Israel*
[2]*Bruce Rappaport Faculty of Medicine,, Technion Israel Institute of Technology,, Haifa,, Israel*
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[6]*Faculty of Medicine,, Ben Gurion University,, Beer Sheva, Israel*
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[9]*Faculty of Medicine,, Hebrew University of Jerusalem,, Jerusalem, Israel*

10:00-10:12 **T1D Virtual Multidisciplinary Patient Centered Care Improves Glycemic and Patient Reported Outcomes**
Noga Minsky1[,2], Genya Aharon-Hananel[1,2], Amna Jabarin[2,3], Liat Arnon[3], Nicole Morozov[2], Dania Halperin[2], Moshe Shalom[2], Elizabeth Tarshish[4], Tatyana Kolobov[5], Amir Tirosh[1,2], Orly Tamir[5]
[1]*Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel*
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[3]*Pediatric Endocrinology and Diabetes, Sheba Medical Center, Ramat Gan, Israel*
[4]*Health Management, Ariel Univeristy, Ariel, Israel*
[5]*The Pesach Segal Israeli Center for Diabetes Research and Policy, Gertner Institute for Epidemiology and Health Policy Research, Ramat Gan, Israel*

10:12-10:24 **Hyperglucagonaemia in Diabetes: Altered Amino Acid Metabolism Triggers mTORC1 Activation Which Drives Glucagon Production**

Yael Riahi[1], Aviram Kogot-Levin[1], Liat Kadosh[1], Bella Agranovich[2], Assaf Malka[3], Michael Assa[3], Ron Piran[3], Dana Avrahami[1], Benjamin Glaser[1], Eyal Gottlieb[2], Fields Jackson III[4], Erol Cerasi[1], Ernesto Bernal Mizrachi[5], Aharon Helman[4], Gil Leibowitz[1]

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[3] *The Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel*
[4] *Department of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, Hebrew University, Rehovot, Israel*
[5] *Department of Internal Medicine, Division of Endocrinology, Metabolism and Diabetes, Miller School of Medicine, University of Miami, Miami FL, USA*

10:24-10:30 **Discussion**

09:00-10:30 **Parallel Session:**
Abstracts: Pituitary and thyroid **Hall B**
Chair: Dr Shlomit Koren, Shamir Medical Center
Dr. Uri Yoel, Soroka Medical Center

09:00 - 09:12 **Increased Cancer Risk in Acromegaly Patients – The Never Ending Controversy**

Hadar Duskin-Bitan[1,2], Alon Perez[3,4], Doron Netzer[3], Arnon D. Cohen[3], Doron Comaneshter[3], Tanya Beckenstein[3], Shlomit Yaron[3], Yaron Rodman[1], Hiba Masri Iraqi[1], Ilan Shimon[1]

[1] *Sackler School of Medicine, Tel-Aviv University, Institute of Endocrinology, Beilinson Hospital, Petach Tikva, Israel*
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[3] *Community Medical Services, Clalit Health Services Division, Tel Aviv, Israel*
[4] *School of Public Health, University of Haifa, Haifa, Israel*

09:12 - 09:24 **Hemoglobin Decline as a Signal for Hyperprolactinemia Onset Prior to Prolactinoma Diagnosis in Hypogonadal Men**

Yaron Rudman[1,2], Hadar Duskin-Bitan[1,2], Ilan Richter[2,3], Gloria Tsvetov[1,2], Hiba Masri-Iraqi[1,2], Amit Akirov[1,2], Ilan Shimon[1,2]

[1] *Institute of Endocrinology, Beilinson Hospital, Rabin Medical Center, Petah-Tikva, Israel*
[2] *Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3] *Department of Cardiology, Rabin Medical Center, Petah-Tikva, Israel*

09:24 - 09:36 **Association Between COVID-19 Immunization or Infection and Thyroiditis: A Population-Based Study**

Hadar Duskin-Bitan[1,2], Alon Peretz[2,3], Alex Gorshtein[1], Tanya Beckenstein[2,] Doron Netzer[2], Arnon D Cohen[2], Walid Saliba[4], Ilan Shimon[1], Eyal Robenshtok[1]

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[3] *School of Public Health, University of Haifa, Haifa, Israel*
[4] *Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*

09:36 - 09:48 **COVID-19 vaccination and Graves' disease: a population based, matched case-control study**

Alexander Gorshtein[1,2], Adi Turjeman[2,3], Hadar Duskin-Bitan[1,2], Leonard Leibovici[2,3], Eyal Robenshtok[1,2]

[1] *Endocrinology, Rabin Medical center, Petah Tikva, Israel*
[2] *Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3] *Research Authority, Rabin Medical center, Petah Tikva, Israel*

09:48 - 10:00 **Glycerol Phenylbutyrate Treatment for Monocarboxylate Transporter 8 (MCT8) Deficiency**

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Pediatric Endocrinology Unit, Kaplan Medical Center, Rehovot, Israel

10:00 - 10:12 **The association between maternal TSH levels and pregnancy outcomes in hypothyroid women**

Tamar Eshkoli[1], Nitzan Burrack[2], Adi Gordon-Irshai[2], Uri Yoel[1], Merav Fraenkel[1]

[1] *Endocrinology Unit, Soroka University Medical Center, Beer-Sheva, Israel*
[2] *Soroka Clinical Research Center, Soroka University Medical Center, Beer-Sheva, Israel*

10:12 - 10:24 **Are Higher BMI and Worse Metabolic Parameters Associated with More Aggressive Differentiated Thyroid Cancer? A Retrospective Cohort Study**

Yasmin Abu Arar[1], Michael Shilo[2], Natalia Bilenko[2], Hagit Marsha[3], Merav Fraenkel[3,4], Uri Yoel[3,4]

[1] *Internal Medicine D, Soroka University Medical Center, Beer Sheva, Israel*
[2] *Epidemiology, biostatistics and community health sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[3] *Health sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[4] *Endocrinology, Soroka University Medical Center, Beer Sheva, Israel*

10:24 - 10:30 **Discussion**

09:00-10:30 Parallel Session:
Abstracts: reproduction, sex hormones **Hall C**
Chair: Prof. Eran Gershon, Volcani Institute
Prof. Ruth Shalgi, Tel Aviv University

09:00 - 09:12 **Foxl2 and Nr5a1 Regulation in Differentiating and Mature Gonadotrope Cells in the Anterior Pituitary**

Hadas Gruber[1], Gil Golan[1], Tal Refael[1], Lilach Pnueli[1], Philippa Melamed[1]

Biology, Technion - Israel Institute of Technology, Haifa, Israel

09:12 - 09:24 **Mechanisms involved in the protective effect of carotenoids, polyphenols, and estradiol in human skin cells under mitochondrial oxidative stress**

Aya Darawshe, Yoav Sharoni

Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Beer-Sheva, Israel

09:24 - 09:36 **Single Cell Analysis of Postnatal Pituitary Stem Cell Differentiation to Gonadotropes**
Gil Golan[1], Daniel Sheridan[2], Karine Rizzoti[2], Robin Lovell-Badge[2], Philippa Melamed[1]
[1]Faculty of Biology, Technion-Israel Institute of Technology, Haifa, ISRAEL
[2]Francis Crick Institute, Francis Crick Institute, London, UK

09:36 - 09:48 **A high-throughput screen reveals novel regulation of MKRN3 in GnRH secreting mouse neurons via the activin receptor pathway**
Dor Shalev[1], Lilach Pnueli[1], Gil Golan[1], Yael Mandel Gutfreund[1], Philippa Melamed[1]
Faculty of Biology, Technion israel institute of technology, Haifa, Israel

09:48 - 10:00 **The Role of Pigment Epithelium-Derived Factor in Folliculogenesis**
Rana Tarabeih[1], Luba Nemerovsky[1], Hadas Ben-Joseph[2], Anat Eldar-Boock[2], Cindy Elmechaly[1], Ido Ben-Ami[3], Ruth Shalgi[1]
[1]Cell and Developmental Biology, Medical School, Tel Aviv University, Tel Aviv, Israel
[2]The TMCR Unit, Medical School, Tel Aviv University, Tel Aviv, Israel
[3]IVF and Infertility Unit, Department of Obstetrics and Gynecology,, Shaare Zedek Medical Center, The Hebrew University Medical School, Jerusalem, Israel

10:00 - 10:12 **TGFβ1 Role in Fine Balancing Ovulation**
Dafna Ketter[1], Nitzan Rimon[1], Michal Neeman[1], Nava Dekel[1]
Immunology and Regenerative Biology, Weizmann Institute of Science, Rehovot, Israel

10:12 - 10:24 **Sirt-1 Activator for Treatment of Post-Menopausal Hepatic Steatosis**
Neta Offir[1,2], Irina Gurt[1], Rivka Dresner-Pollak[1,2], Joshua Stokar[1,2,3]
[1]Endocrinology, Hadassah Medical Center, Jerusalem, Israel
[2]Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
[3]Internal Medicine Mount Scopus, Hadassah Medical Center, Jerusalem, Israel

10:24 - 10:30 **Discussion**

10:30-11:00 Coffee Break & Exhibition

11:00-12:20 **Plenary Session** **Hall A**
Chair: Prof. Gil Leibowitz, Hadassah Medical Center
Dr. Yael Kuperman, Weizmann Institute of Science

11:00-11:15 **Greetings**
Prof. Gil Leibowitz, President, Israel Endocrine Society
Dr. Yael Kuperman, Conference Chairperson

11:15-11:30 **Grants Summary**
Prof. Rivka Dresner-Pollak, Dr. Rena Pollack Hadassah Medical Center
Dr. Reut Halperin, Prof. Amit Tirosh Sheba Medical center

11:30-12:20 **Host microbiome interaction in health and disease**
Prof. Eran Elinav
Head, Systems Immunology Department, Weizmann Institute of Science, Israel

12:20-13:30 **Change Halls**

12:30-13:45 **Parallel Session** **Hall B**
Nutrient sensing
Chair: Dr. Yoav Livneh, Weizmann Institute of Science
Prof. Amir Tirosh, Sheba Medical Center

12:30-12:55 **Mapping the hypothalamic feeding circuitry using single-cell approaches**
Prof. Giles Yao
MRC Metabolic Diseases Unit, University of Cambridge, UK

12:55-13:20 **Brain-body interactions: sensations and predictions in the insular cortex**
Dr. Yoav Livneh
Depatment of Brain Sciences Weizmann Institute of Science, Israel

13:20-13:45 **Clues in the reward system of the brain for the susceptibility to overeat**
Prof. Yonatan Kupchik
Department of Medical Neurobiology, Institute for Medical Research Israel-Canada (IMRIC) Center for Addiction Research (ICARe), Faculty of Medicine, The Hebrew University of Jerusalem, Israell

12:30-13:45 **Parallel Session** **Hall C**
Thyroid and Pregnancy: Have we finally reached a consensus on this?
Chair: Dr. Yoel Toledano, Rabin Medical Center
Prof. Dania Hirsch, Rabin Medical Center

12:30-12:55 **TSH and Pregnancy: Finding Your Way Out of the Gray Zone**
Dr. Tim Korevaar
Department of Internal Medicine and the Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands

12:55-13:20 **Infertility Risk and Pregnancy Rate in Female Thyroid Cancer Survivors**
Prof. Dania Hirsch
Institute of Endocrinology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

13:20-13:45 **A Gland-Mass Model: How the Thyroid Axis is Compensated by Gestational Dynamics?**
Dr. Alon Bar
Department of Molecular cell biology, Weizmann Institute of Science, Israel

13:45-14:45 **Lunch & Exhibition**

14:45-16:00 **Parallel Session: Guided Poster Sessions**

Guided Poster Sessions: Diabetes **Hall A**
Chair: Dr. Ronny Helman, The Hebrew University of Jerusalem
Dr. Alex Gurshtein, Rabin Medical Center

14:45 - 14:52 **Drug-drug interactions between glucagon-like peptide 1 receptor agonists and oral medications: a systematic review**
Bronya Calvarysky[1,2], Idit Dotan[3,4], Avi Leader[4,5], Talia Diker Cohen[3,4]
[1]Pharmacy, Beilinson Hospital, Rabin Medical Center, Petah-Tikva, Israel
[2]Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
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[4]Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel
[5]Institute of Hematology, Beilinson Hospital, Rabin Medical Center, Petah-Tikva, Israel

14:52 - 15:00 **What causes Fasting Hyperglycemia in Pre-Diabetes?**
Sarah Knapp[1], Danny Ben-Zvi[2]
[1]Human Genetics in Bio-Medical Science, The Institute for Medical Research Israel-Canada, The Hebrew University-Hadassah Medical School, Jerusalem, Israel
[2]Developmental Biology and Cancer Research, The Institute for Medical Research Israel-Canada, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

15:00 - 15:07 **Mood and Personality Changes After Bariatric Surgery in Diabetes Patients**
Yael Sofer[1], Shirley Roitmann[2], Shai Eldar[3], Subhia Abu-Abeid[4], Guy Lahat[3], Iosef Koriansky[23], Danit Dayan[3], Sigal Fishman[5], Matti Shnell[5], Esther Osher[1], Miri Margaliot[1], Nofar Yerushalmi[1], Naftali Stern[1], Odelia Elkana[2]
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[5]Bariatric Endoscopy Service, Department of Gastroenterology and Liver Disease, Tel Aviv Sourasky Medical Center, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

15:07 - 15:15 **The effect of hypokalemia during the treatment of diabetic ketoacidosis. A retrospective, single-center analysis**
Said Darawshi[1], Irit hokhberg[2], Asaf Miller[3], Majd Qassum[4]
[1]Internal medicine D, Rambam medical center, Haifa, Israel
[2]Endocrinology department, Rambam medical center, Haifa, Israel
[3]Intensive care unit, Rambam medical center, Haifa, Israel
[4]Cardiology depratment, Rambam medical center, Haifa, Israel

15:15 - 15:22 **Safety and efficacy of non-insulin therapy in hospitalized patients with type 2 diabetes mellitus – a systematic review and meta-analysis of randomized control trials**
Irit Ayalon-Dangur[1], Tanya Babich[2,3], Maayan Huberman[4], Leonard Leibovici[3,5], Alon Grossman[2,6]
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[2]Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel
[3]Research Authority, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel
[4]Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel
[5]Sackler Faculty of Medicine, Tel Aviv University, Petah-Tikva, Israel
[6]Department of Medicine B, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel

15:22 - 15:30 **The impact of chronobiological disorders on gestational diabetes mellitus outcomes: The Chrono-Nutrition Gestational Diabetes Study**
Amalia Messika[1], Yoel Toledano[1]
Helen Schneider Hospital for Women, Rabin Medical Center, Petach Tikva, Israel

15:30 - 15:37 **Monogenic Diabetes Multigene Panel Results in Patients Selected on Clinical Basis- far beyond the 7 genes**
Michal Levine[1], Mais Narar Halihal[1,2], Vitaly Medvedovsky[1,3], Idit Liberty[4,5], Uri Yoel[1,5], Merav Fraenkel[1,5]
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[2]Kupat holim, Mehuhedet, Sotuthern district, Israel
[3]Faculty of health science, Ben Gurion University of the Negev, Sotuthern district, Israel
[4]Diabetes Clinic, Soroka University Medical center, Be'er Sheva, Israel
[5]Faculty of health science, Ben Gurion University of the Negev, Be'er Sheva, Israel

15:37 - 15:45 **Israel National Wolfram Syndrome Registry**

Noga Minsky[1,2], Liat Arnon[1], Eve Stern[2,3], Merav Fraenkel[4,5], Lior Greebaum[2,6], Orit Pinhas-Hamiel[2,3]

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[6]*The Danek Gertner Institute of Human Genetic, Sheba Medical Center, Ramat Gan, Israel*

15:45 - 15:52 **Modeling the effects of maternal type 1 diabetes on embryonic development in mice**

Ronny Helman[1]

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

15:52 - 16:00 **Discussion**

Guided Poster Sessions: Bone, calcium metabolism and growth **Hall B**

Chair: Dr. Vanessa Rouach, Tel Aviv Sourasky Medical Center
Dr. Liana Tripto Shkolnik, Sheba Medical Center

14:45 - 14:53 **Increased Fracture Risk Among Children and Adolescents with Celiac Disease: A Nation Wide Cohort Study**

Galia Zacay[1,2], Ilana Weintrob[1,2,3], Dalit Modan-Moses[1,2,4], Yael Levy-Shraga[1,2,4]

[1]*Meuhedet, Health Services, Tel aviv, Israel*
[2]*Sackler School of Medicine, University of Tel Aviv, Tel aviv, Israel*
[3]*Pediatric Gastroentrology, The Edmond and Lily Safra Children's Hospital, Ramat Gan, Israel*
[4]*Pediatric Endocrinology and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Ramat Gan, Israel*

14:53 - 15:01 **A single center experience with opportunistic diagnosis of osteoporosis by artificial intelligence-the time has come**

Yehonatan Beeri[1], Gal Ben-Arie[2,3], Ilan Shelef[2,3], Merav Fraenkel[3,4]

[1]*Goldman School of Medicine Faculty of Health Science, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[2]*Radiology, Soroka University Medical Center, Beer-Sheva, Israel*
[3]*Faculty of Health Science, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[4]*Endocrinology, Soroka University Medical Center, Beer-Sheva, Israel*

15:01- 15:09 **Normocalcemic primary hyperparathyroidism is an early stage of pimary hyperparathyroidism according to Fibroblast Growth Factor -23 level.**

Elena Chertok Shacham, Nimra Maman, Tatyana Lazareva, Gala Sela, Refaat Masalha, Lila Mahagna, Avraham Ishay

[1]*Endocrinology Unit, Haemek Medical Center, Afula, Israel*
[2]*Statistical department, Haemek Medical Center, Afula, Israel*
[3]*Internal medicine department A, Haemek Medical Center, Afula, Israel*
[4]*Laboratory medicine department, Haemek Medical Center, Afula, Israel*
[5]*Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel*

15:09- 15:17 **Clinical and Molecular Characteristics and Long-term Follow-up of Children with Pseudohypoparathyroidism Type 1A.**

Hanna Ludar[1], Yael Levy-Shraga[2,3], Osnat Admoni[4], Hussein Majdoub[5], Kineret Mazor Aronovitch[2,3], Ilana Koren[1], Shoshana Rath[4,6], Ghadir Elias-assad[7,8], Shlomo Almashanu[9], Giovanna Mantovani[10,11], Orit Pinhas Hamiel[2,3], Yardena Tenenbaum-Rakover[12,13,10]

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[6]*Endocrinology and Diabetes Service, Tzafon Medical Center, Teveria, Israel*
[7]*Pediatric Health Center, Clalit Health Services, Afula, Israel*
[8]*Pediatric Endocrine Institute, Saint Vincent Hospital, Nazareth, Israel*
[9]*The National Newborn Screening Program, Ministry of Health, Ramat Gan, Israel*
[10]*Endocrinology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[11]*Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy*
[12]*Consulting Medicine in Pediatric Endocrinology, Clalit Health Services, Afula, Israel*
[13]*The Rappaport Faculty of Medicine, Technion, Institute of Technology, Haifa, Israel*

15:17 - 15:26 **Teriparatide Treatment of osteoporosis in Solid Organ Transplant Recipients – a single-center experience**

Talia Diker Cohen[1,2], Gloria Tsvetov[1,2]

[1]*Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

15:26 - 15:34 **Parathyroid Hormone Levels Following Denosumab Therapy vs. Zoledronic Acid Therapy For Osteoporosis**

Pnina Rotman Pikielny[1,2], Tzipi Hornik Lurie[3], Liat Barzilai-Yosef[1], Erez Ramaty[1], Sofia Braginski-Shapira[1], Michal Kasher-Miron[1,2]

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[2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Research Institute, Meir Medical Center, Kfar Saba, Israel*

15:34 - 15:42 **The Variant Tyr 394Ser in the GCM2 Gene is Rare in a Cohort of Ashkenazi Jews with Primary Hyperparathyroidism**

Lior Tolkin[1], Vanessa Klein[1], Meir Frankel[1], Gheona Altarescu[2], Rachel Beeri[2], Gabriel Munter[1]

[1]*Endocrinology unit, Shaare zedek medical center, Jerusalem, Israel*
[2]*Genetic unit, Shaare zedek medical center, Jerusalem, Israel*

15:42 - 15:50 **Compromised Adult Height In Females With Non-Classical Congenital Adrenal Hyperplasia Diagnosed In Childhood**
Rachel Bello[1,2], Liora Lazar[1,2], Moshe Phillip[1,2], 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, Petah Tikva, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

15:50 - 16:00 **Discussion**

Guided Poster Sessions: Thyroid and lipids **Hall C**
Chair: Dr. Rachel Rosenblum, Wolfson Medical Center
Dr. Elena Itzhakov, Tel Aviv Sourasky Medical Center

14:45 - 14:52 **Cardiac biomarkers in Fabry disease exhibit distinct associations with cardiovascular outcomes: A (Rare) Prism for Cardiovascular Endocrinology**
Elad Shemesh[1], Rosemary Rusk, Patrick Deegan
Institute of Endocrinology and Metabolism, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

14:52 - 15:00 **Non Interventional Weight Changes Are Associated With Alterations In Lipid Profile And In Triglyceride To HDL-Cholesterol Ratio**
Shiri Weinstein[1,2], Elad Maor[2,3], Alon Kaplan[1,2], Avshalom Leibowitz[1,2], Ehud Grossman[1,2], Gadi Shlomai[1,2,4]
[1]*Department of Internal Medicine D and Hypertension unit, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel*
[2]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Leviev Heart Center, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel*
[4]*the Institute of Endocrinology, Diabetes and Metabolism, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel*

15:00 - 15:07 **Adipose Tissue Support Of Cancer Growth Is Mediated By The Adipokine FABP4**
Rinat Livne[1], Reem Igbaria[1,2], Amit Tirosh[1,2], Amir Tirosh[1,2]
[1]*The Dalia and David Arabov Endocrinology and Diabetes Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Ramat Gan, Israel*
[2]*Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*

15:07 - 15:15 **Association between Body Mass Index, Thyroid Cancer, and Weight Change: A Longitudinal Follow-Up Study.**
Dania Hirsch[1,2], Michal Yackobovitch-Gavan[3,4], Adi Turjeman[5], Liora Lazar[2,3]
[1]*Institute of Endocrinology, Rabin Medical Center, Petach Tikva, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*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*
[4]*Deptartment of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[5]*The Research Authority, Rabin Medical Center, Petach Tikva, Israel*

15:15 - 15:22 **Microscopic Calcifications Isolated from Thyroid Nodule Fine Needle Aspiration Can Serve as Biomarkers of Thyroid Nodule Malignancy- A Proof of Concept Study**
Uri Yoel[1,2], Lotem Gotnayer[3], Dina Aranovich[3], Netta Vidavsky[3], Merav Fraenkel[1,2]
[1]*Endocrinology, Soroka University Medical Center, Beer Sheva, Israel*
[2]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[3]*Department of Chemical Engineering, Ben-Gurion University of the Negev, Beer Sheva, Israel*

15:22 - 15:30 **Long-term metabolic outcomes in Graves` disease: Is there a difference between oral anti-thyroid medications and radioactive iodine treatment?**
Elad Shemesh, Tamara Kolitz[1], Alexandra Nathan[1], Karen Tordjman[1], Yona Greenman[1], Elena Izkhakov[1]
Institute of Endocrinology and Metabolism, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

15:30 - 15:37 **Serological Profile in Rheumatoid Arthritis and its Interplay with Autoimmune Thyroid Diseases**
Tamara Kolitz[1], Shaye Kivity[2,3], Idit Tessler[3,4], Yonit Marcus[1,3], Yona Greenman[1,3]
[1]*Institute of Endocrinology, Diabetes, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2]*Rheumatology Unit, Meir Medical Center, Kfar Saba, Israel*
[3]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[4]*Department of Otolaryngology, Head, and Neck Surgery, Sheba Medical Center, Ramat Gan, Israel*

15:37 - 15:45 **Immune checkpoint inhibitors and severe insulinopenic diabetes mellitus: a single center experience**
Ruth Karov[1], Tamara kolits, Eugene Feigin, Roy Eldor, Michal Ehrenwald, Yona Greenman
The institution of endocrinology diabetes metabolism and hypertension, Tel Aviv-Sourasky Medical Center, Tel-Aviv, Israel

15:45 - 15:52 **LMF1 Associated Chylomicronemia Syndrome**
Michal Yacobi Bach[1,2], Merav Serebro[1], Hagit Baris Feldman[2], Yona Greenman[1]
[1]*Endocrinology Department, Tel Aviv Medical Center, tel aviv, Israel*
[2]*Genetics Department, Tel Aviv Medical Center, tel aviv, Israel*

15:52 - 16:00 **Differentiation of Gastric Corpus Enteroendocrine Cells (gEEC), Including L Cells**
Amit Elad[1], Danny Ben-Zvi[1], Rachel Schyr[1]
Faculty of Medicine, Hebrew University, Jerusalem, Israel

Guided Poster Sessions: Metabolism, reproduction, and gender **Hall 3**
Chair: Prof Liat de Vries, Schneider Children's Medical Center of Israel
Dr. Iris Yaish, Tel Aviv Sourasky Medical Center

14:45 - 14:52 **Novel Cis-Regulatory Mechanisms of Lhb Transcription by Non-Coding RNAs and Non-Canonical DNA Structures**
Tal Refael[1], Hadas Gruber[1], Lilach Pnueli[1], Philippa Melamed[1]
Biology, Technion, Haifa, Israel

14:52 - 15:00 **The increase in DHEA and its role in reproduction maturation: insights from the spiny mouse model**
Maya Sudman[1], Hadas Gruber[1], Philippa Melamed[1]
Faculty of Biology, Technion - Israel Institute of Technology, Haifa, Israel

15:00 - 15:07 **Over-Representation of Adoptees among Transgender Subjects Seeking Gender-Affirming-Hormonal-Therapy (GAHT) in a Large Tertiary Medical Center.**
Iris Yaish[1], Gali Keltch[2], Yona Greenman[3], Karen Tordjman[3]
[1]The Transgender Health Center, Institute of Endocrinology, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]The Academic College of Tel Aviv-Yaffo, Tel Aviv, Israel, School of Behavioral Science, Tel Aviv, Isreal
[3]The Transgender Health Center, Institute of Endocrinology, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Isreal

15:07 - 15:15 **Differences in Sex Development – The Clinical Experience of a Tertiary Care Center**
Amit Eben Chaime[1], Moshe Phillip[1,2], David Ben-Meir[2,3], Liat de Vries[1,2]
[1]Institute for Endocrinology and Diabetes, Schneider's Children Medical Center, Petach Tikva, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Pediatric Urology Unit, Schneider's Children Medical Center, Petach Tikva, Israel

15:15 - 15:22 **CNS Manifestations are Linked with Hot Flashes: Analysis of Real-World Data from a Social Network**
Sigal Shaklai[1,2], Yona Greenman[1,2], Elad Yom-Tov[3]
[1]Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel
[2]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[3]Faculty of Industrial Engineering and Management, Technion, Haifa, Israel

15:22 - 15:30 **Glucocorticoid Resistance Syndrome: A Challenging Diagnosis**
Dima Namouz[1], Michal Yacobi Bach[1,2], Michal Gershinsky[3,4], Yona Greenman[1,5]
[1]Institute of Endocrinology, Diabetes, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]Genetics Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Department of Endocrinology and Diabetes, Lady Davis Carmel Medical Center and Linn Medical Center, Clalit Health Services, Haifa, Israel
[4]Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel
[5]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

15:30 - 15:37 **Body composition in pediatric celiac disease and metabolic syndrome component risk-an observational study**
Anat Yerushalmy-Feler[1,2], Oren Kassner[2], Yael Frank[2], Hadar Moran-Lev[1,2], Adi Anafy[1,2], Dina Levy[1], Hagar Interator[3], Erella Elkon-Tamir[2,3], Shlomi Cohen[1,2], Yael Lenenthal[2,3], Avivit Brener[2,3]
[1]Pediatric Gastroenterology, Dana Dwek Children's Hospital, Tel Aviv, Israel
[2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Pediatric Endocrinology, Dana Dwek Children's Hospital, Tel Aviv, Israel

15:37 - 15:45 **Deciphering Liver Glycome Regulation by the PGC-1/FN3K Axis**
Efrat Glick-Saar[1], Amir Tirosh[2], Neri Minsky[2]
[1]Wohl Institute for Translational Medicine, Sheba Medical Center, Ramat-Gan, Israel
[2]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Ramat-Gan, Israel

15:45 - 15:52 **Cardiovascular Outcomes of Glucose-lowering Pharmacological Agents in Older Adults-Systematic Review and Meta-analysis**
Hanna Taleisnik Halimi[1], Tali Cukierman-Yaffe[2,3]
[1]Department of Nutrition and Dietetics, Sheba Medical Center, Ramat Gan, Israel
[2]Division of Endocrinology & Metabolism, Sheba Medical Center, Ramat Gan, Israel
[3]Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

15:52 - 16:00 **Glucagon-like peptide 1 receptor agonists and cardiovascular outcomes in solid organ transplant recipients with diabetes mellitus**
Idit Dotan[1,2], Yaron Rudman[1,2], Adi Turjeman[2,3], Amit Akirov[1,2], Bronya Calvarysky[4,5], Talia Diker Cohen[1,2]
[1]Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel
[3]Research Authority, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel
[4]Pharmacy, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel
[5]Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Guided Poster Sessions: Pituitary, neuroendocrine tumors **Hall 4**
Chair: Dr. Etty Osher, Tel Aviv Sourasky Medical Center
Dr. Leonid Michael, Assuta Medical Centers

14:45 - 14:52 **Xenograft of VHL-deficient pancreatic neuroendocrine neoplasm cells - a novel low-grade PNEN in vivo model**
Alona Telerman[1], Yuval Yossef[1,2], Adiel Chmelnik[1,2], Amit Tirosh[1,2]
[1]*ENTIRE-Endocrine Neoplasia Translational Research Center, Sheba Medical Center, Ramat Gan, Israel*
[2]*Medicine, Tel Aviv University, Tel Aviv, Israel*

14:52 - 15:00 **Trajectories of Pituitary Height and Endocrine Function in survivors of childhood and adolescence brain tumors.**
Larisa Gorenstein[1], Gadi Abebe-Campino[2,3], Michal Ben-Ami[3,4], Eve Stern[3,4], Michal Yalon[3,5], Shani Caspi[3,5], Shai Shrot[3,6], Dalit Modan[3,4]
[1]*Diagnostic Imaging, Sheba Medical Center, Ramat-Gan, Israel*
[2]*Pediatric Hemato-Oncology, Sheba Medical Center, Ramat-Gan, Israel*
[3]*Sackler faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel*
[4]*Pediatric Endocrinology, Sheba Medical Center, Ramat Gan, Israel*
[5]*Pediatric Hemato-Oncology, Sheba Medical Center, Ramat Gan, Israel*
[6]*Diagnostic Imaging, Sheba Medical Center, Ramat Gan, Israel*

15:00 - 15:07 **Controlling gene expression in gastric endocrine cells using Adeno-Associated virus**
Botros Moalem, Danny Ben Zvi[1], Rachely Schyr[1], Amit Elad[1]
developmental biology and cancer research, hebrew university of jerusalem, jerusalen, Israel

15:07 - 15:15 **Can radiation absorbed doses after 177Lu-PRRT be estimated from a single SPECT/CT study: Validation of a MLR model and impact on patient management for 192 therapies**
Alexandre Chicheportiche[1], Yodphat Krausz[1], Jeremy Godefroy[1], David J. Gross[2], Simona Grozinsky-Glasberg[2], Simona Ben-Haim[1]
[1]*Department of Nuclear Medicine & Biophysics, Hadassah Medical Organization, Jerusalem, Israel*
[2]*Neuroendocrine Tumor Unit, ENETS Center of Excellence, Endocrinology and Metabolism Department, Hadassah Medical Organization, Jerusalem, Israel*

15:15 - 15:22 **Single-Nucleus RNA sequencing-based characterization of sporadic and VHL related Pancreatic Neuroendocrine Neoplasms (PNEN)**
Yuval Yossef[1], Alona Telerman[2], Amit Tirosh[2]
[1]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[2]*ENTIRE - Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Metabolism and Diabetes, Sheba Medical Center, Ramat Gan, Israel*

15:22 - 15:30 **Mid-treatment Response to 177Lu-DOTATATE Predicts Overall Treatment Outcome in Patients With Neuroendocrine Neoplasms**
Reut Halperin[1,2], Amit Tirosh[1,2]
[1]*ENTIRE– Endocrine Neoplasia Translational Research Center, Division of Endocrinology, Metabolism and Diabetes, Sheba Medical Center, Ramat Gan, Israel*
[2]*Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

15:30 - 15:37 **Reversible Pro-oncogenic Effect of Netrin - DCC Interaction on Neuroendocrine Neoplasm Cells**
Liav Sela-Peremen[1,2], Sapir Nasirov[1,2], Yuval Yosef[1,2], Liel Getahon[1], Ali Aborya[1], Alona Telerman[1,3], Amit Tirosh[1,3]
[1]*ENTIRE center, Sheba medical center, Ramat-Gan, Israel*
[2]*Faculty of Medicine, Tel Aviv university, Tel Aviv, Israel*
[3]*Faculty of medicine, Tel Aviv University, Tel-Aviv, Israel*

15:37 - 15:45 **The Effect of a Pseudohypoxic Environment on the Immune System of Pancreatic Neuroendocrine Tumors (PanNET)**
Adiel Chmelnik Solomon[1], Alona Telerman[2], Amit Tirosh[3]
[1]*ENTIRE Center, Tel Aviv University Faculty of Medicine, Ramat Gan, Israel*
[2]*ENTIRE Center, Sheba Medical Center, Ramat Gan, Israel*
[3]*ENTIRE Center, Tel Aviv University and Sheba Medical Center, Ramat Gan, Israel*

15:45 - 15:52 **Langerhans Cell Histiocytosis With Hypothalamo-Pituitary Involvement: The HEROS Study**
Hiba Masri Iraqi[1,2], Marina Tsoli[3], Annamaria Colao[4], Diego Ferone[6], Miklós Tóth[5], Ekaterina Pigarova[7], Amit Akirov[1,2], Lior Baraf[8], Yona Greenman[2,9], Mirjana Doknic[10], Gregory Kaltsas[3], Ilan Shimon[1,2]
[1]*Endocrinology, Rabin Medical Center, Petah Tiqva, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Pathophysiology Department, LAIKO HOSPITAL, Athens, Greece*
[4]*Department of Medicine Clinica e Chirurgia, Univ. Federico II di Napoli, Napoli, Italy*
[5]*Semmelweis University, Semmelweis University, Budapest, Hungary*
[6]*Endocrinology Unit, University of Genova, Genova, Italy*
[7]*Endocrinology, Endocrinology Research Centre, Moscow, Russia*
[8]*Endocrinology, Soroka University Medical Center, Beer Sheva, Israel*
[9]*Endocrinology department, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel*
[10]*Neuroendocrine Department, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*

15:52 - 16:00 **Impulse Control Disorders in Patients with Prolactinomas and Non-Functioning Pituitary Adenomas Treated with Dopamine Agonists**
Elad Shemesh[1], Tamara Kolitz[1], Alexandra Nathan[1], Roy Eldor[1,2], Elena Izkhakov[1,2], Yona Greenman[1,2]
[1]*Institute of Endocrinology, Diabetes, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

Guided Poster Sessions: Obesity and diabetes — **Hall 5**
Chair: Dr. Ido Goldstein, The Hebrew University of Jerusalem
Dr. Yael Sofer, Tel Aviv Sourasky Medical Center

14:45 - 14:52 **Prediabetes in pregnancy Diabetes – outcomes compared to type 2 diabetes**
Tal Schiller[1,2], Oren Barak[2,3,4,5], Yael Winter Shafran[2,3], Miri Barak Sacagiu[2,3], Lee Cohen[1,2], Edi Vaisbuch[2,3], Taiba Zornitzki[1,2], Alena Kirzhner[1,2,6]
[1]Institute of Endocrinology, and Metabolic Disease, Kaplan Medical Center, Rehovot, Israel
[2]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel
[3]Department of Obstetrics and Gynecology, Kaplan Medical Center, Rehovot, Israel
[4]Department of Obstetrics, Gynecology and Reproductive Science, University of Pittsburgh School of Medicine, Pittsburgh, USA
[5]Magee-Womens Research Institute, University of Pittsburgh School of Medicine, Pittsburgh, USA
[6]Department of Medicine, Kaplan Medical Center, Rehovot, Israel

14:52 - 15:00 **The Role of Adipocyte Connexin-43 in Mediating Adipose Tissue Inflammation and Dysfunction in Obesity**
Sophie Ron[1,2], Idit Ron[1], Moran Rathaus[1], Rinat Livne[1], Yulia Haim[3], Amit Tirosh[1,2], Assaf Rudich[3], Amir Tirosh[1,2]
[1]The Dalia and David Arabov Endocrinology and Diabetes Research Center, Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel-Hashomer, Israel
[2]Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel
[3]Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel

15:00 - 15:07 **Sex differences in body composition in youth with type 1 diabetes and its predictive value in cardiovascular disease risk assessment**
Avivit Brener[1,2], Sandy Hamma[2], Hagar Interator1, Asaf Ben Simon[2], Irina Laurian[1], Anna Dorfman[1], Efrat Chorna[1], Michal Yackobovitch-Gavan[2], Asaf Oren[1,2], Ori Eyal[1,2], Yael Lebenthal[1,2]
[1]Pediatric Endocrinology, Dana Dwek Children's Hospital, Tel Aviv, Israel
[2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

15:07 - 15:15 **The metabolic role of Somatostatin in sleeve gastrectomy**
Doron Kleiman[1], Yhara Arad[1], Mika Littor[2], Rachel Ben-Haroush Schyr[1], Danny Ben-Zvi[1]
[1]Department of Developmental Biology and Cancer Research, Institute of Medical Research Israel-Canada, The Hebrew University-Hadassah Medical School, jerusalem, Israel
[2]Department of Military Medicine and "Tzameret", Faculty of Medicine, Hebrew University of Jerusalem, and Medical Corps, Israel Defense Forces, jerusalem, Israel

15:15 - 15:22 **Persistent Post-Bariatric-Surgery Hypoglycemia: a Long Term Follow up Reassessment**
Viviana Ostrovsky, Hilla Knobler, Li Or Lazar, Guy Pines, Tamila Kuniavsky, Lee Cohen, Tal Schiller, Alena Kirznher, Taiba Zornitzki
[1]Diabetes, Endocrinology and Metabolic Disease Institute, Kaplan Medical Center, Hebrew University Medical School, Rehovot, Israel
[2]Surgery Department, Kaplan Medical Center, Hebrew University Medical School, Rehovot, Israel

15:22 - 15:30 **Phytocannabinoids for Treating Obesity-Related Non-Alcoholic Fatty Liver Disease**
Radka Kocvarova[1], Shahar Azar, Yossi Tam
School of Pharmacy, the Hebrew University of Jerusalem, Jerusalem, Israel

15:30 - 15:37 **Renal Mitochondrial ATP Transporter Ablation Ameliorates Obesity-induced Chronic Kidney Disease**
Anna Permyakova[1], Sharleen Hamad1, Liad Hinden[1], Saja Baraghithy[1], Aviram Kogot-Levin[2], Omri Yosef[3], Abhishek Basu[4], Muhammad Arif[4], Resat Cinar[4], George Kunos[5], Michael Berger[3], Gil Leibowitz[2], Joseph Tam[1]
[1]Pharmacology, The Hebrew University of Jerusalem, Jerusalem, Israel
[2]Diabetes, The Hebrew University of Jerusalem, Jerusalem, Israel
[3]Immunology, The Hebrew University of Jerusalem, Jerusalem, Israel
[4]Fibrotic Disorders, National Institutes of Health, Rockville, United States
[5]Physiologic Studies, National Institutes of Health, Rockville, United States

15:37 - 15:45 **Is leptin resistance in pregnancy a result of the tightening of the blood-brain barrier in the hypothalamus?**
Aviv Halfon[1], Danny Ben-Zvi[1], Ayal Ben-Zvi[1]
Department of developmental biology and cancer research, The Hebrew University- Faculty of Medicine,, Hebrew University of Jerusalem, Jerusalem, Israel

15:45 - 15:52 **The role of the Insular Cortex in the anticipatory insulin response**
Einav Litvak[1], Yoav Livneh[1]
Brain Sciences Department, Weizmann Institute of Science, Rehovot, Israel

15:52 - 16:00 **Discussion**

16:00-16:30 **Break & Exhibition**

16:30-17:15 **Plenary Session** — **Hall A**
Chair: Prof. Orit Hamiel, Sheba Medical Center
Dr. Idit Dotan, Rabin Medical Center

16:30-17:15 **Is obesity a choice?**
Prof. Giles Yao
MRC Metabolic Diseases Unit, University of Cambridge, UK

17:20-18:00 **Parallel Sessions: Meet the Expert** — **Hall B**
Chair: Dr. Tamar Eshkoli, Soroka Medical Center
Dr. Orit Barenholtz, Shaare Zedek Medical Center

Challenging Case Studies on Thyroid and Pregnancy
Dr. Tim Korevaar
Department of Internal Medicine and the Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands

17:20-18:00 **Parallel Sessions: Meet the Expert** — **Hall C**
Chair: Dr. Liat Barzilay, Meir Medical Center
Dr. Taiba Zornitzki, Kaplan Medical Center

Why doctors aren't nice-burnout as a challenge for healthcare organizations in the 21st century
Dr. Dror Dolphin
Deputy Director General, Soroka Medical Center

19:00-21:00 **Satellite Symposium + Dinner – pre registration only**
Benefits in treating obesity and diabetes, beyond glycemic control and weight.
Sponsored by NovoNordisk

Tuesday, May 23, 2023

07:00-09:00 **Satellite Symposium + Breakfast – pre registration only**
Diabetes, sarcopenia and aging- challenges and management.
Sponsored by AstraZeneca

07:30-08:30 **Registration, Refreshments & Exhibition**

08:30-10:00 **Parallel Session:**
Abstracts - Diabetes, obesity and metabolism 2 — **Hall A**
Chair: Dr. Hannah Kanety, Sheba Medical Center
Prof. Danny Ben-Zvi, The Hebrew University of Jerusalem

08:30-08:42 **Diagnosis of Overweight or Obesity and its Association with Performance Rates of Obesity Care in the Primary Care Setting**
Michal Kasher Meron[1,2], Sapir Eizenstein[2], Dan Oieru[2,3]
[1]*Department of Endocrinology, Meir Medical Center, Clalit Health Service, Kfar Saba, Israel*
[2]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Family Medicine, Maccabi Healthcare Services, Tel Aviv, Israel*

08:42-08:54 **The Psychoactive Drug 5-Methoxy-2-aminoindane (MEAI) is a Novel Regulator of Energy Metabolism and Obesity**
Saja Baraghithy[1], Asaad Gammal[1], Sharleen Hamad[1], Radka Koscvarova[1], Yael Calles[1], Joseph Tam[1]
Obesity and Metabolism Laboratory, The Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

08:54-09:06 **Discovery and Experimental Confirmation of a Novel Obesity-related Kidney-to-Liver Axis**
Sharleen Hamad[1], Anna Permyakova[1], Yossi Tam[1]
Obesity and Metabolism Laboratory, The Institute for Drug Research, School of Pharmacy, Faculty of Medicine,, The Hebrew University of Jerusalem, Jerusalem, Israel

09:06-09:18 **Circulating "Inflammo-miRNAs": a "liquid biopsy" approach to detect human obesity phenotypes with high versus low visceral adipose tissue inflammation**
Nataly Makarenkov[1], Yulia Haim[1], Uri Yoel[2,3], Yair Pincu[1], Tanya Tarnovscki[1], Idit Liberty[4], Ivan Kukeev[5], Oleg Dukhno5, Matthias Blüher[6], Assaf Rudich[1], Isana Veksler-Lublinsky[7]
[1]*Clinical Biochemistry and Pharmacology, Ben-Gurion University, Beer Sheva, Israel*
[2]*Endocrinology, Soroka University Medical Center, Beer Sheva, Israel*
[3]*Faculty of health sciences, Ben-Gurion Universiry, Beer Sheva, Israel*
[4]*Diabetes clinic, Soroka University Medical Center, Beer Sheva, Israel*
[5]*Surgery B, Soroka University Medical Center, Beer Sheva, Israel*
[6]*University Hospital Leipzig, University of Leipzig, Leipzig, Germany*
[7]*Software and Information Systems Engineering, Ben-Gurion University, Beer Sheva, Israel*

09:18-09:30 **Novel Peripherally Restricted Cannabinoid-1 Receptor Blockers for Treating Diet-induced Obesity and its Metabolic Complications**

Asaad Gammal[1,2], Yael Soae[3], Amit Badihi[4], Noam Freeman[4], taher nassar[5], simon benita[5], yossi tam[6]

[1]1Obesity and Metabolism Laboratory, Faculty of Medicine, The Hebrew University, Jerusalem, Israel
[2]2Laboratory of Nano Delivery Systems, Faculty of Medicine, The Hebrew University, Jerusalem, Israel
[3]3BioNanoSim (BNS), Hadassah Ein Kerem Campus, Jerusalem, Israel
[4]BioNanoSim (BNS), Hadassah Ein Kerem Campus, Jerusalem, Israel
[5]Laboratory of Nano Delivery Systems, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
[6]Obesity and Metabolism Laboratory, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

09:30-09:42 **Inherited Stress Resiliency Prevents the Development of Metabolic Alterations in Diet-Induced Obese Mice**

Michaella Ben-Shachar[1], Saumya Mehta[1], Sharmila Govindaraj[1], Albert Pinhasov[1,2], Tovit Rosenzweig[1,2]

[1]Molecular Biology, Ariel University, Ariel, Israel
[2]Adelson School of Medicine, Ariel University, Ariel, Israel

09:42-09:54 **Weight Regain Following Bariatric Surgery and In Vitro Fertilization Outcomes**

Bar Zemer tov[1,2], Tomer Ziv-Baran[3], May Igawa[2,4], Gabriella Lieberman[2,5], Raoul Orvieto[2,4], Ronit Machtinger[2,4]

[1]Infertility and IVF Unit, Department of Obstetrics and Gynecology, Sheba Medical Center, Ramat Gan, Israel
[2]faculty of medicine, Tel Aviv university, Tel Aviv, Israel
[3]Department of Epidemiology and Preventive Medicine, Tel Aviv university, Tel Aviv, Israel
[4]Infertility and IVF Unit, Department of Obstetrics and Gynecology, Sheba medical center, Ramat Gan, Israel
[5]Department of Endocrinology, Sheba medical center, Ramat Gan, Israel

09:54-10:00 **Discussion**

08:30-10:00 **Parallel Session:**
Abstracts - Sex hormones/menopaouse/adrenal **Hall B**
Chair: Dr. Leonard Saiegh, Bnai Zion Medical Center
Dr. Sigal Shaklai, Tel-Aviv Sourasky Medical Center

08:30 - 08:42 **Predictive value of ovarian reserve parameters for follicle detection in ovarian tissue cryopreservation**

Noah Gruber[1,2], Michal Zajicek[2,3], Alexander Volodarsky-Perel[2,4], Daniel Shai[2,4], Daniela Dick-Necula[2,5], Hila Raanani[2,3], Gideon Karplus[2,6], Eran Kassif[2,4], Boaz Weisz[2,4], Dror Meirow[2,3]

[1]Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel
[2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Fertility Preservation Center, Department of Obstetrics and Gynecology, Sheba Medical Center, Ramat Gan, Israel
[4]Institute of Obstetrics and Gynecological Imaging and Fetal Therapy, Department of Obstetrics and Gynecology, Sheba Medical Center, Ramat Gan, Israel
[5]Department of Pathology, Sheba Medical Center, Ramat Gan, Israel
[6]Department of Pediatric Surgery, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel

08:42 - 08:54 **Sublingual Estradiol Offers no Advantage Over Combined Oral Estradiol and Cyproterone Acetate for Gender Affirming Hormone Therapy of Treatment-Naïve Transwomen: Results of a Prospective Pilot Study.**

Guy Gindis[1,2], Iris Yaish[1], Yona Greenman[1,2], Yaffa Moshe[1], Mira Arbiv[1], Assaf Buch[1], Yael Sofer[1,2], Gabi Shefer[1], Karen Tordjman[1,2]

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

08:54 - 09:06 **Serum Adropin is Reduced in Post-Menopausal Women**

Joshua Stokar[1,2,3], Murad Daana[1,2], Ghadeer Zatarah[1], Rivka Dresner-Pollak[1,3]

[1]Endocrinology, Hadassah Medical Center, Jerusalem, Israel
[2]Internal Medicine Mount Scopus, Hadassah Medical Center, Jerusalem, Israel
[3]Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

09:06 - 09:18 **Is there seasonal variation in testosterone levels? Data from a large cohort of men**

Taiba Zornitzki[1], Sagi Tshori[2], Galit Shefer[2], Shira Mingelgrin[2], Carmit Levy[3], Hilla Knobler[4]

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09:18 - 09:30 **Body composition in children and adolescents with non-classic congenital adrenal hyperplasia and the risk for components of metabolic syndrome: An observational study**

Adi Uretzky[1], Avivit Brener, Asaf Ben Simon, Anat Segev-Becker, Michal Yackobovitch-Gavan, Anita Schachter Davidov, Angelika Alaev, Asaf Oren, Ori Eyal, Naomi Weintrob, Yael Lebenthal

pediatric endocrinology, ichilov, tel aviv, israel

09:30 - 09:42 **Genotype-Specific Cortisol Reserve in a Large Cohort of Subjects with Non-Classic Congenital Adrenal Hyperplasia (NCCAH)**

Ilana koren[1,2], Anat Segev-Becker[3], Nili Stein[4], Rebeca Kabash[5], Hussein Magdoub[5], Naomi Weintrob[6]

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[6]Pediatric Endocrinology, Dana Dwek Children's Hospital, Tel Aviv Medical Center, Tel aviv, Israel

09:42 - 09:54 **A 120-Minute Saline Infusion Test for the Confirmation of Primary Aldosteronism**

Tiran Golani[1,2], Jonathan Bleier[1,2], Alon Kaplan[1,2], Tamar Hod1,[3,4], Yehonatan Sharabi[1,2], Avshalom Leibowitz[1,2], Ehud Grossman[1,2], Gadi Shlomai[1,2,5]

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09:54 - 10:00 **Discussion**

08:30-10:00 **Parallel Session:**
Abstracts: Bone and neuroendocrine tumors **Hall C**
Chair: Prof. Simona Glasberg, Hadassah Medical Center
Prof. Amit Tirosh, Sheba Medical Center

08:30 - 08:42 **Hyperglycemia-Induced Unique Transcriptional Changes in Osteocytes**

Joshua Stokar[1,2], Vladislav Temkin[1], Irina Gurt[1], Natan Lishinsky[1,2], Lynne Cox[3], Rivka Dresner Pollak[1,2]

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[2]*Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*
[3]*Department of Biochemistry, University of Oxford, Oxford, United Kingdom*

08:42 - 08:54 **Burosumab therapy in children with X-linked hypophosphatemia: a real-life long-term study**

Yael Levy-Shraga[1], Shelly Levi[2], Ravit Regev[3], Shoshana Gal[4], Avivit Brener[5], Yael Lebenthal[5], David Gillis[6], David Strich[7], Amnon Zung[8], Zvi Zadik[8], Roxana Cleper[9], Yael Borovitz[10], Miriam Davidovits[10], Leonid Zeitlin[11], Dov Tiosano Tiosano[12]

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08:54 - 09:06 **The association between antiresorptive therapy, fracture risk and mortality in osteoporotic patients with concurrent type II diabetes mellitus: a large, population-based cohort study.**

Vanessa Rouach[1,2,3], Hilary Gortler[3], Yona Greenman[3,4], Gabriel Chodick[5,6], Inbal Goldshtein[5,6]

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[6]*Israel Maccabitech Institute for Research and Innovation, Maccabi Healthcare Services, Tel aviv, Israel*

09:06 - 09:18 **Distinct Growth Characteristics in Angelman Syndrome**

Ayman Daka[1,2], Gali Heimer[2,3], Noy Lapidot[1,2], Bruria Ben Zeev[2,3], Dalit Modan-Moses[2,4], Orit Pinhas-Hamiel[2,4], Noah Gruber[1,2,4]

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09:18 - 09:30 **Novel Calcium-Sensing Receptor (CASR) Mutation in a Family with Autosomal Dominant Hypocalcemia Type 1 (ADH1): Genetic Study over Three Generations and Clinical Characteristics**

Amnon zung[1], Galia Barash[2], Ehud Banne[3], Michael A. Levine[4]

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[2]*Pediatric Endocrinology Unit, Shamir (Assaf Harofeh) Medical Center, Tzrifin, Israel*
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[4]*Center for Bone Health and Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA*

09:30 - 09:42 **Engaging the Endocannabinoid System to Overcome Drug Resistance in Neuroendocrine Neoplasms (NENs)**

Shani Polak[1], David Polak[2], Yotam Drier[3], Simona Glasberg[1]

[1]*Department of Endocrinology and Metabolism Neuroendocrine tumor unit, Hadassah Medical Center, Jerusalem, Israel*
[22]*Department of Periodontics, Dental Medicine Faculty, Hadassah Medical Center, Jerusalem, Israel*
[3]*The Faculty of Medicine, Lautenberg Center for Immunology and Cancer Research, The Hebrew University, Jerusalem, Israel*

09:42 - 09:54 **Efficiency of Somatostatin Analogues (SSA) as adjuvant treatment to prevent recurrence of neuroendocrine tumours (NETs) post-surgery**

Daniel Abramov[1], Simona Grozinsky-Glasberg[1]

Neuroendocrine Tumor Unit, ENETs Center of Excellence, Department of Endocrinology and Metabolism, Hadassah Medical Organization and Faculty of Medicine, Jerusalem, Israel

09:54 - 10:00 **Discussion**

10:00-10:30 **Coffee Break & Exhibition**

10:30-12:15 **Parallel Session** — **Hall B**
Neuroendocrinology and beyond
Chair: Prof. Tovit Rosenzweig, Ariel university
Prof. Naomi Weintraub, Tel Aviv Sourasky Medical Center

10:30-11:00 **Brown Fat and Cardiometabolic Health**
Prof. Paul Cohen
Laboratory of Molecular Metabolism, The Rockefeller University, USA.

11:00-11:30 **New diagnostic and therapeutic options in patients with AVP-deficiency**
Prof. Mirjam Christ-Crain
Department of Endocrinology, University Hospital Basel, University of Basel, Switzerland

11:30-11:50 **Developmental underpinnings of neuroendocrine functions: lessons from zebrafish**
Prof. Gil Levkowitz
Department of Molecular Cell Biology and Molecular Neuroscience, Weizmann Institute of Science, Israel

11:50-12:15 **Advances in the treatment of CAH from birth to adulthood**
Prof. Richard Ross
Department of Oncology and Metabolism, The University of Sheffield, UK

10:30-12:15 **Parallel Session** — **Hall C**
NAFLD & cluster T2D / Women health
Chair: Dr. Joelle Singer, Rabin Medical Center
Dr. Tal Ben Ari, Wolfson Medical Center

10:30-11:00 **Pathogenetic links between severe insulin resistant diabetes and NAFLD**
Dr. Oana-Patricia Zaharia
Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research. Department of Endocrinology and Diabetology, Medical Faculty and University Hospital, Heinrich-Heine University, Düsseldorf, Germany

11:00-11:30 **Nonalcoholic fatty liver disease -The forgotten complication of diabetes**
Prof. Hila Knobler
Diabetes Institute, Meuhedet, Faculty of Medicine, Hebrew University School of Medicine, Jerusalem, Israel

11:30-12:15 **The metabolic memory of lactation–endocrine facts and challenges**
Deena Zimmerman M.D. IBCLC
Director Maternal Child and Adolescent Department Public Health Division Israel Ministry of Health
Active board member of the Israeli Association of Breastfeeding Medicine
International Board Certified Lactation Consultant
Moran Friedman M.D. IBCLC
Family Physician, Clalit Health Services, Haifa, Israel
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Association of Breastfeeding Medicine Active board member of the Israeli
International Board Certified Lactation Consultant

12:15-13:15 **Lunch & Exhibition**

13:15-13:55 **Plenary Session** — **Hall A**
Chair: Prof. Philippa Melamed, Technion - Israel institute of technology
Dr. Avivit Brener, Dana Dwek Children's Hospital, Tel Aviv Sourasky Medical center

13:15-13:55 **GnRH and cognition in Down Syndrome**
Prof. Nelly Pitteloud
Chief of Endocrinology, University Hospital Lausanne, Switzerland

13:55-15:00 **Plenary Session** — **Hall A**
IES Prize session
Chair: Prof. Gil Leibowitz, Hadassah Medical Center
Dr. Merav Fraenkel, Soroka Medical Center

The Chowers Award: Dr. Rana Halloun and Dr. Ido Goldstein
The Lindner Award: Prof. Gilad Twig
The Uri Liberman Award: Dr. Iris Vered
Best Mentor Award: Prof. Nava Bashan and Prof. Naftali Stern
Best Community Physician Award: Dr. Rosane Abramof Ness

15:00-15:20 **Coffee Break & Exhibition**

15:20-16:20 **Parallel Session** — **Hall A**
Graves' Disease: New Insights and Guidelines
Chair: Dr. Eyal Robenshtok, Rabin Medical Center
Dr. Sagit Zolotov, Rambam Medical Center

15:20-15:35 **Treatment of Graves' Disease: What's New?**
Prof. Eyal Robenshtok
Endocrinology & Metabolism Institute, Rabin Medical Center, Israel

15:35-15:50 **The Immunologic Side of TED**
Prof. Nancy Agmon-Levin
Clinical Immunology, Angioedema and Allergy Unit, Sheba Medical Center, Israel

15:50-16:20 **Case Discussions – Graves' Disease and Pregnancy, TED**
Case 1: Dr. Yonit Marcus
Case 2: Prof. Tali Cukierman-Yaffe
Panel: Dr. Rina Pollack,Prof. Tali Cukierman-Yaffe / Dr. Yonit Marcus, Dr. Inbal Avisar, Prof. Eyal Robenshtok, Dr. Tamar Eshkoli

15:20-16:10 **Parallel Session** — **Hall B**
Stem cells and cell-fate
Chair: Prof. Mike Walker, Weizmann Institute of Science
Prof. Yuval Dor, The Hebrew University of Jerusalem

15:20-15:50 **Modeling sex differences in humans using isogenic induced pluripotent stem cells**
Prof. Benny Reubinoff
Director of the Sidney and Judy Swartz Stem Cell Research Center, The Department of Obstetrics and Gynecology, The Goldyne Savad Institute of Gene Therapy, Hadassah Medical Center, Ein Kerem, Jerusalem, Israel

15:50-16:10 **Becoming a pituitary gonadotrope: epigenetics and lineage speciation**
Prof. Philippa Melamed
Technion - Israel institute of technology

16:10-16:20 **Change Halls**

16:20-17:20 **Parallel Session: Meet The Expert** — **Hall B**
Syndrome of inappropriate antidiuresis (SIAD) – diagnosis andtreatment
Chair: Dr. Merav Fraenkel, Soroka Medical Center
Prof. Amit Akirov, Rabin Medical Center

Syndrome of inappropriate antidiuresis (SIAD) – diagnosis and treatment
Prof. Mirjam Christ-Crain
Department of Endocrinology, University Hospital Basel, University of Basel, Switzerland

16:20-17:20 **Parallel Session: Meet The Expert** — **Hall C**
New frontiers in nutrition
Chair: : Prof. Yoav Sharoni, Ben-Gurion University of the Negev
Dr. Galia Gat-Yablonski, Felsenstein Medical Research Center

16:20-16:50 **Sustainable healthy nutrition as the compass coping with the interlinkage syndemia and climate crisis**
Dr. Dorit Adler
President of the Israeli Forum for Sustainable Nutrition and Co-Chair food Systems cluster - The Israeli Climate Forum

16:50-17:20 **The effect of eating patterns on bone development and quality**
Prof. Efrat Monsonego
Institute of Biochemistry and Nutrition, The Faculty of Agriculture, Food and Environment
The Hebrew University of Jerusalem, Israel

Invited Speakers

Dr. Paul Cohen
USA

Prof. Mirjam Christ-Crain
Switzerland

Prof. Nelly Pitteloud
Switzerland

Dr. Oana Patricia Zaharia
Germany

Dr. Tim Korevaar
Netherlands

Prof. Giles Yao
UK

Prof. Richard JM Ross
UK

ABSTRACTS

Monday, May 22, 2023

09:00-10:30 22.5 Parallel Sessions: Abstracts: Diabetes , obesity and metabolism 1, Hall A - abstract session - day one

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Mapping the Metabolic Reprogramming Induced by Sodium-glucose Cotransporter 2 Inhibition

Aviram Kogot-Levin[1], Dr. Yael Riahi[1], Prof. Ofri Mosenzon[1], Mrs. Ifat Abramovich[2], Mrs. Bella Agranovich[2], Mrs. Liat Kadosh[1], Dr. Rachel Ben-Haroush Schyr[3], Mr. Doron Kleiman[3], Prof. Erol Cerasi[1], Dr. Liad Hinden[4], Prof. Danny Ben-Zvi[3], Prof. Joseph Tam[4], Prof. Eyal Gottlieb[2], Prof. Gil Leibowitz[1]

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[4]*Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Israel*

Introduction: SGLT2 inhibitors (SGLT2i) reduce the risk for kidney disease, congestive heart failure and mortality in patients with and without diabetes. We have previously shown that the beneficial effects of SGLT2i are mediated via inhibition of the nutrient sensor mTORC1 in renal proximal tubular cells (RPTCs). We hypothesize that RPTCs function as a metabolic hub, regulating nutrient(s) metabolism in various organs. Here, we aimed to decipher the metabolic alterations that occur in the kidney, liver, and heart in diabetes and in response to SGLT2 inhibition, which prevent glucose reabsorption in RPTCs.

Methods. We performed *in vivo* metabolic labeling with $^{13}C_6$-glucose in normoglycemic wild-type and diabetic Akita mice treated with or without the SGLT2 inhibitor dapagliflozin (10 mg/kg/day) or degludec insulin (1-4 units/day) for one week, followed by simultaneous metabolomics and metabolic flux analyses in the kidney cortex, liver, heart, and the plasma. mTORC1 and AMPK activities were analyzed by Western blotting.

Results: We found that in diabetes, glycolysis and glucose oxidation are impaired in the kidney, liver, and heart, evident by decreased levels of ^{13}C-labeled pyruvate, lactate and TCA cycle metabolites. Treatment with dapagliflozin failed to rescue glycolysis and further inhibited pyruvate kinase activity in the liver. On the contrary, SGLT2 inhibition increased glucose oxidation in all organs. In addition, dapagliflozin increased plasma and liver ketone body β-hydroxybutyrate levels. Diabetes was associated with altered methionine cycle metabolism, evident by decreased betaine and methionine levels, whereas treatment with SGLT2i increased hepatic betaine along with decreased homocysteine levels. The activity of mTORC1 was inhibited by SGLT2i along with stimulation of AMPK in both normoglycemic and diabetic animals. In contrast to SGLT2i, treatment with insulin enhanced glycolysis, glucose-derived amino acid synthesis and inhibited ketogenesis.

Conclusions: SGLT2i induce metabolic reprogramming orchestrated by the key nutrient-sensing pathways AMPK and mTORC1, leading to enhanced energy production through increased glucose and fatty-acid oxidation, whereas insulin promote energy-consuming anabolic pathways. In addition, SGLT2i prevent dysregulated methionine cycling in diabetes. These effects may explain the beneficial effects of SGLT2i with important implications for diabetes and aging.

Obesity in patients with youth-onset T2D: the Israeli cohort

Nehama Zuckerman - Levin[1,2], Dr. Meidan Cohen[1,2], Prof. Moshe Phillip[3,4], Dr. Ariel Tenenbaum[3,4], Dr. Ilana Koren[2,5], Prof. Yardena Tenenbaum-Rakover[2,6], Dr. Osnat Admoni[6], Prof. Eli Hershkovitz[7,8], Dr. Alon Haim[7,8], Dr. Kineret Mazor Aronovitch[4,9,10], Prof. David Zangen[11,12], Prof. David Strich[12,13], Dr. Avivit Brener[4,14], Dr. Yonatan Yeshayahu[8,15], Dr. Yossi Schon[16], Prof. Marianna Rachmiel[4,16], Dr. Tal Ben-Ari[4,17], Dr. Floris Levy-Khademi[12,18], Dr. Afif Nakhleh[1,2], Dr. Rami Tibi[1,2], Prof. Ram Weiss[1,2], Prof. Yael Lebenthal[4,14], Prof. Orit Pinhas-Hamiel[4,9,10], Prof. Naim Shehadeh[1,2,19]

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Introduction:

The incidence of youth-onset T2D has increased significantly worldwide, paralleling the rise in pediatric obesity. A recent Israeli registry examined the demographic and clinical manifestations of T2D in children and adolescents. The current study focuses on the role of obesity in its development.

Methods:

This national observational study included 14 pediatric diabetes clinics in Israel . Participants were children and adolescents, aged 10-18 years with a diagnosis of T2D according to the ADA criteria. Demographic, clinical, and laboratory data were obtained from their medical records, covering the period between 2008 and 2019.

Results:

The study cohort consisted of 379 patients, with 228 (59.7%) being female and 221 (58.3%) being Jews.The mean age of the participants at diagnosis was 14.7±1.9 years. A positive family history of T2D was found in 73.1% of the patients. At the time of diagnosis, 32% of the patients required hospitalization (P0.001), while 42.3% were asymptomatic (P=0.002), with a higher occurrence in Arab youth. The mean A1c level at diagnosis was 8.8 ± 2.5% (73 ± 4 mmol/mol). Obesity, defined as a BMI percentile greater than 95th (BMI z-score 1.645), was found in 77% of the patients (mean BMI z-score = 1.96 ± 0.7), with a higher prevalence

in Jews compared to Arabs. Higher A1c at diagnosis was associated with a lower BMI z-score. 62.2% of the T2D patients met the modified IDF criteria for metabolic syndrome. Fatty liver was documented in 65% of the patients, primarly among Jews.

Conclusions:

This study revealed that not all youth with T2D had obesity, indicating that factors beyond obesity may play a role in the development of T2D in this population. To gain a deeper understanding of the origin of T2D in this group, further investigation is required with a specific emphasis on exploring the role of ethnicity.

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The cytokine SDF-1 and its receptors regulate liver metabolism – a fresh look on intrahepatic communication

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Type 2 Diabetes (T2D) imposes an enormous socioeconomic burden on modern society. Dysregulation of liver metabolism is a significant contributor to the pathophysiology of T2D due to its importance in controlling whole-body glucose and fat metabolism. Importantly, T2D and the related insulin resistance are closely associated with the development of Nonalcoholic Fatty Liver Disease (NAFLD) and its progression to nonalcoholic steatohepatitis (NASH). Identifying new mechanisms that regulate liver metabolism is critical for understanding how whole-body metabolic homeostasis is maintained and will pave the way for designing new treatments for T2D and metabolic diseases. Here, we investigate the importance of the cytokine SDF-1, whose primary source in the liver is the non-parenchymal cells (NPCs), in regulating liver metabolism. Our preliminary data show that SDF-1 and its receptors, CXCR4 and CXCR7, are strongly regulated in the liver in response to physiologic fasting and refeeding, suggesting an involvement in modulating the fasting-refeeding transition. Moreover, the SDF-1/CXCR4/CXCR7 pathway is dysregulated in diabetic mice, further implying a connection to T2D pathophysiology. Interestingly, mouse models in which the SDF-1/CXCR7/CXCR4 pathway is manipulated show strong effects on liver glucose and fat homeostasis. We propose that SDF-1, secreted from liver NPCs, modulate liver metabolic homeostasis by acting directly on hepatocytes. These findings highlight the importance of the cross-talk between NPCs and hepatocytes in the metabolic regulation of the liver.

Gut microbiota and physical capacity in older people with diabetes

Naama Peltz-Sinvani[1], Dr Michal Azmon[1,2], Mrs Tal Yahalom Peri[1], Mrs Yamit Bason[1], Prof Tali Cukierman-Yaffe[1,3]

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Aim

1. To evaluate the association between physical capacity indices (aerobic, balance, strength) and gut microbiota composition in older people with diabetes.

2. To assess the difference in gut microbiota composition of older people with diabetes that are frail/pre-frail and non-frail individuals.

Background

Both diabetes and aging are risk factors for disability, frailty, and an accelerated decline in physical capacity, due partly to lower muscle quality, mass, and strength.

Gut microbiota composition changes with aging and diabetes and may be associated with muscle strength and function.

However, most data regarding relationship between gut microbiota, sarcopenia and disability comes from animal studies.

Methods:

A cross-sectional study. Data regarding demographics and diabetes-related variables were collected from 90 individuals ≥60years with diabetes. Participants underwent an elaborate assessment of frailty status and physical capacity indices (strength, balance, and aerobic capacity) and stool samples were collected. Participants were divided according to their performance into 3 groups- intact, mild, and severe physical impairment. Fecal samples underwent microbial DNA extraction, amplification, and in-silico metagenomics.

For the continuous parameters, the diversity analysis was followed by linear regression to analyze the directionality of the interaction between the dissimilarities and the continuous parameters.

For gut microbiome differential abundance analysis, DESeq2, R/bioconductor package was used. Rarified scaled ASVs were labeled by the lowest assigned taxa level possible and were summarized per taxa. Differential abundance between conditions was assessed and significant taxa (p-adjusted values0.05 and |log2foldchange|=0.58) were used to build heatmaps, generated using pheatmap.

Results:

This analysis pertains to 90 older individuals with diabetes, mean age 71.2±7.75years, mostly males (61.1%), mean diabetes duration 17.7±10.7years.

Fusicatenibacter was more abundant in the intact+mild vs severe physical impairment group, in females. Genus Prevotella was positively correlated with better scores on the hand grip test (dominant and non-dominant hand, p0.05). Genus Monoglobus was positively correlated with better scores on 6MW test (p0.05).

A positive correlation between the non-dominant hand-grip score and beta-diversity was shown (R=0.054, p=0.00061). There was a positive correlation between the 6MW score and beta-diversity (R=0.075, p=2e-06).

Conclusions:

In this cohort we found that Fusicatenibacter was associated with better physical performance in females. A positive correlation between 2 bacterial genera and certain physical indices was found. In the literature, genus Fusicatenibacter is known to produces anti-inflammatory short-chain fatty acid butyrate, genus Prevotella was positively correlated with better functioning scores. Less is known about genus Monoglobus. Further studies are needed to further validate these findings.

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Diabetologist Training Program for Family Physicians in Israel: 2017-2022

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Introduction: In Israel, over half a million people live with diabetes, and there are less than 200 endocrinologists that treat all endocrine disorders, including diabetes. Most people with diabetes are treated in a community setting by family physicians, and many are not treated optimally. Therefore, there is a solid need to train many family physicians as diabetologists.

Methods: In 2017, a joint effort of the Israeli Endocrine Society, the Israeli Council for Diabetes, the Israeli Association of Family Physicians, and the Israeli Society for Internal Medicine launched a national training program in diabetes for specialists in family medicine and internal medicine. The Israeli Medical Association Scientific Council (IMA-SC) approved the course. The training program includes an academic course of 130 hours (weekly lectures and practice sessions and periodic half-day workshops) followed by a written examination; supervised clinical training for 350 hours (8 hours per week for one year) at an approved diabetes clinic and two weeks in a hospital setting.

Results: During 2017-2022, 285 physicians completed the academic course, 145 attended the clinical training year in 35 diabetes clinics, and 95 completed two weeks of in-hospital training and received a certificate approved by IMA-SC. Of all course participants, 143 physicians (50.2% of the 285 trainees) answered an online questionnaire. Of the physicians that responded, 54.2% women with a mean (SD) age of 45.9 (8.9) years, 52.4% are specialists in family medicine, and 35.7% were specialists in internal medicine. The physicians are distributed nationwide; 28.7% work in the north, 30.8% in the center, 20.3% in the south, and 7.0% in Jerusalem and the west bank. Amongst the 107 physicians who work predominantly in the community, 64.5% worked in Clallit, 23.4% in Maccabi, 6.5% in Leumit, and 5.6% in Meuchedet. The mean (SD) overall satisfaction from the course was 9.0/10.0 (1.4) without significant differences between courses where the lectures were held frontally compared to courses where the lectures were primarily held virtually by Zoom (p=0.738). Only 26.6% of the graduates stated that they currently work as a “diabetologist.”

Conclusion: While a two-year, part-time training of family and internal medicine specialists in diabetes is feasible, for various reasons, most trainees have not yet been given the time or position to work as diabetologists. How to optimize the efficient use of the trainees is currently being investigated.

T1D Virtual Multidisciplinary Patient Centered Care Improves Glycemic and Patient Reported Outcomes

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Lack of access to specialized multidisciplinary teams, familiar with advanced technologies for T1D care, has been a barrier to achieving glycemic targets and other patient-centered goals in Israel. Since launching a hospital-based T1D virtual clinic in 2018, our team of endocrinologists, nurses, dieticians, social workers and clinical coordinators we have treated 145 adults with T1D. We report outcomes, over the first year in our service, for the first 114 patients who had previously received standard care. Mean age upon recruitment was 42±14 years, 40% were females. Sixty percent were from the Tel Aviv and Central districts, 31% from Haifa and North districts, with the rest distributed evenly between remaining districts. At baseline, 88% had insulin pumps (8% hybrid closed loop) and 93% had CGM or FGM. There were significant improvements in glycemic indices and in validated and self-originated patient reported outcome measures at 6 and 12 months as compared to baseline (table 1). Mean baseline HbA1c was 8.1%, and this improved to 7.6% and 7.3% at 6 and 12 months respectively (p 0.001). Average sensor glucose declined by 5.5% over 6 months (p0.001). While TIR increased significantly by 10.4%, TBR decreased. Diabetes Treatment Satisfaction Questionnaire scores improved significantly, as did Diabetes Self-Management Questionnaire scores assessing diabetes self-care behaviors. According to survey responses, transitioning to virtual care was associated with improved satisfaction with the availability of the physician, nurse and dietitian beyond the appointment time and with the guidance received beyond scheduled visits. Remote care allowed patients to save time and reduce expenses by lessening the frequency of office visits. In conclusion, transitioning from standard T1D care to remote multidisciplinary care prompts improved glycemic control and higher patient satisfaction and better self-care behaviors.

Table1. Glycemic Measures and Patient Reported Outcomes Measures according to Validated Questionnaires

			12 months
Measured HbA1c (%)	8.1	7.6*	7.3*
Average Sensor glucose (mg/dl)	163	154*	157*
% Time in target range (70-180mg/dl)	61.6	68.3*	68.0*
% Time below range (54-70mg/dl)	3.7	3.2	2.7*
% Time below range (54mg/dl)	1.4	1.3	0.9*
% Time above range (181-250mg/dl)	21.9	19.9*	20.2
% Time above range (250mg/dl)	10.6	7.5*	8.4*

DTSQ- Treatment Satisfaction	26.7	30.3*	30.7*
DSMQ- Diabetes Self-Management	7.0	7.2	7.4*

*P 0.05 (P values reflect comparison to baseline measures using a Student t-test)

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Hyperglucagonaemia in Diabetes: Altered Amino Acid Metabolism Triggers mTORC1 Activation Which Drives Glucagon Production

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Aim/Hypothesis Hyperglycaemia is associated with alpha-cell dysfunction leading to dysregulated glucagon secretion in type 1 and type 2 diabetes, however the mechanisms involved are still elusive. The nutrient sensor mammalian target of rapamycin complex 1 (mTORC1) plays a major role in the maintenance of alpha-cell mass and function. We studied the regulation of the alpha-cell mTORC1 by nutrients and its role in the development of hyperglucagonaemia in diabetes.

Methods Alpha-cell-mTORC1 activity was assessed by immunostaining for the phosphorylation of its downstream target, the ribosomal protein S6 (pS6) and glucagon, followed by confocal microscopy on pancreatic sections and flow cytometry on dispersed human and mouse islets and the alpha-cell line, αTC1-6. Metabolomics and metabolic flux analysis was studied by 13C glucose labeling at 2.8 or 16.7 mmol/l followed by LC-MS analysis. To study the role of mTORC1 in mediating the hyperglucagonaemia of diabetes, we generated an inducible alpha-cell specific Raptor knockout in diabetic Akita mice and tested the effects on glucose tolerance by intra-peritoneal glucose tolerance test and glucagon secretion.

Results mTORC1 activity was increased in alpha-cells from diabetic Akita mice in parallel to the development of hyperglycaemia and hyperglucagonaemia (2-8 fold increase). Acute exposure of rodent and human islets to amino acids, stimulated (3.5 fold increase), whereas high glucose inhibited (1.4 fold decrease) the alpha-cell mTORC1. The mTORC1 response to glucose was abrogated in human and rodent diabetic alpha-cells following prolonged islet exposure to high glucose, resulting in sustained activation of mTORC1, along with increased glucagon secretion. Metabolomics and metabolic flux analysis showed that exposure to high glucose enhanced glycolysis, glucose oxidation, and the synthesis of glucose-derived amino acids. In addition, chronic exposure to high glucose increased the expression of the amino acid transporters Slc7a2 and Slc38a4, along with increased branched-chain amino acids and methionine cycle metabolites (~1.3 fold increase). Finally, conditional Raptor knockout in alpha-cells of adult diabetic animals inhibited mTORC1, thereby inhibiting glucagon secretion (~6 fold decrease) and improving diabetes, despite persistent insulin deficiency.

Conclusions/Interpretation Alpha-cell exposure to hyperglycaemia enhances amino acids synthesis and transport, resulting in sustained activation of mTORC1, thereby increasing glucagon secretion. mTORC1, therefore, plays a major role in mediating the alpha-cell dysfunction of diabetes.

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Increased Cancer Risk in Acromegaly Patients – The Never Ending Controversy

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Introduction: The potential association between acromegaly and cancer has long been hypothesized, with inconsistent study results, some reporting higher prevalence of cancer rates, especially colorectal and thyroid, whereas others show no increase. Cancer screening in acromegaly has been a highly controversial issue.

Objective: To investigate the prevalence of malignant neoplasms in patients with acromegaly, utilizing a large cohort of patients with acromegaly.

Material and methods: A retrospective study was performed between 2000 and 2021. We utilized the database of Clalit Health Services (CHS). Data was collected from records of general community and primary clinics, referral centers as well from hospital care. Medical files were screened for the diagnosis of Acromegaly. A control group of individuals without Acromegaly was randomly selected through 1:3-1:5 matching based on age, sex and primary care practice.

Results: A total of 601 acromegaly patients were first evaluated. After charts validation we ended up with 470 acromegaly patients and 2,330 matched controls. Of them, 54% were males, with mean age at diagnosis of 53 (±16) years. The prevalence of all solid malignancies was greater in acromegaly patients, 21.3% vs 14.8%, [OR] 1.56, CI 1.2-2.0 (p0.01), whereas specific evaluation of different cancers found that only thyroid cancer was more prevalent in patients with acromegaly than in control subjects, 2.8% vs 0.6%, [OR] 5.1, CI 2.3-11.0 (p0.01). Other malignancies showed a tendency for a greater prevalence – colorectal cancer, 3.6% vs 2.8%, [OR] 1.3 (0.7-2.2), prostate cancer, 2.8% vs 1.7% [OR] 1.6, CI 0.8-3.1 and kidney cancer, 1.5% vs 0.8%, [OR] 1.84, CI 0.8-4.4. Lung cancer prevalence was similar between the two groups, while breast cancer was less prevalent among acromegaly patients. There was no increase in the prevalence of hematological malignancies among acromegaly patients. Mortality was significantly higher among acromegaly patients, 21.3% vs 15.7% [OR] 1.45, CI 1.1-1.9 (p 0.003). The risk for various malignancies among acromegaly patients and the matched controls is summarized in Table 1. Seventy-three percent of cancer cases in the acromegaly cohort were diagnosed before or during the first 5 years following acromegaly diagnosis. There was no correlation between IGF-1 levels and risk for malignancy.

Discussion: Overall, solid tumors were more prevalent in a large cohort of acromegaly patients when compared to matched controls. Thus, active cancer screening may be considered for early detection of solid cancers, in particularly thyroid cancer.

Table 1. Cancer risk among cohort patients.

	Acromegaly	Control	OR	p Value
Solid tumors	100 (21.3%)	344 (14.8%)	1.56 (1.2-2.0)	<0.01
Hematologic malignancy	11 (2.3%)	46 (2%)	1.19 (0.6-2.3)	0.61
Breast	12 (2.6%)	79 (3.4%)	0.75 (0.4-1.4)	0.35
Colon	17 (3.6%)	66 (2.8%)	1.29 (0.7-2.2)	0.36
Lung	6 (1.3%)	32 (1.4%)	0.93 (0.4-2.3)	0.87
Prostate	13 (2.8%)	40 (1.7%)	1.63 (0.8-3.1)	0.13
Thyroid	13 (2.8%)	13 (0.6%)	5.07 (2.3-11.0)	<0.01
Kidney	7 (1.5%)	19 (0.8%)	1.84 (0.7-4.4)	0.16
mortality	100 (21.3%)	365 (15.7%)	1.45 (1.1-1.9)	0.003

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Hemoglobin Decline as a Signal for Hyperprolactinemia Onset Prior to Prolactinoma Diagnosis in Hypogonadal Men

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Background

Men harboring prolactinomas frequently suffer from central hypogonadism with secondary anemia. They present insidious and non-specific symptoms of hypogonadism, making it difficult to diagnose the disease and determine its duration. The result is a delay in diagnosis, which may have harmful hormonal and metabolic consequences. We hypothesized that a decrease in hemoglobin (HB) levels prior to prolactinoma diagnosis, may signal hyperprolactinemia onset and estimate disease duration.

Methods

We retrospectively evaluated the pre-diagnosis temporal trends in HB levels of 70 males with prolactinoma, diagnosed from January 2010 to July 2022. Men without hypogonadism, patients that received testosterone, and those with unrelated anemia were excluded.

Results

Sixty-one of seventy men (87%) with prolactinoma presented with hypogonadism, and forty men (57%) had HB levels ≤13.5 g/dl at diagnosis.

We identified 25 patients with “informative” HB curves (mean age, 46.1±14.9 years; median prolactin, 952 ng/ml; median follow-up, 14.0 years), demonstrating an obvious pre-diagnosis HB decrease (greater than 1.0 g/dl), from a pre-diagnosis baseline HB of 14.4±0.3 g/dl to 12.9±0.5 g/dl at diagnosis. The median “low-HB duration” (from the first low HB measurement to hyperprolactinemia diagnosis) was 6.1 years (IQR, 3.3-8.8 years).

In symptomatic patients, we identified a correlation between “low-HB duration” and patient-reported sexual dysfunction duration (n=17, R=0.502, p=0.04). The “low-HB duration” was significantly longer than the reported sexual dysfunction duration (7.0±4.5 vs 2.9±2.5 years, p=0.01).

Conclusions

In our cohort of men with prolactinomas and hypogonadism, we found a marked decrease in HB levels that preceded prolactinoma diagnosis by a median of 6.1 years, with a mean delay of 4.1 years between HB decrease and hypogonadal symptoms appearance. These results suggest that HB decline prior to prolactinoma diagnosis may serve as a marker for hyperprolactinemia onset in a subset of hypogonadal men and allow a more accurate assessment of disease duration.

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Association Between COVID-19 Immunization or Infection and Thyroiditis: A Population-Based Study

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Introduction: COVID-19 infection and immunizations have been implicated in the development of a range of autoimmune diseases, including thyroiditis. However, published data is limited, and based mostly on case reports.

Objective: To evaluate the prevalence and severity of thyroiditis during the Covid-19 period, compared to a defined pre-pandemic time period.

Material and methods: A population-based study of 4.8 million people from the Clalit Health Services database, the largest public healthcare provider organization in Israel, was performed. Data was collected from records of general community and primary clinics, referral centers as well from affiliated hospitals. Inclusion criteria included a new diagnosis of thyroiditis, excluding prior treatment that may interfere with thyroid function tests (such as thyroxin, amiodarone, MMI, steroids or anti-neoplastic drugs), and pregnancy.

Results: Between January 2018 and December 2022, 5944 patients were diagnosed with thyroiditis, of whom 76% were females. During the pre covid-19 period, defined as January 2018 to February 2020, 2,720 patients were diagnosed with thyroiditis (105 per month), and during the covid-19 period, defined as March 2020 to December 2022, 3,224 were diagnosed with thyroiditis (97 per month, NS). BMI for the pre-COVID-19 period population was 27.1, and for the COVID-19 group 26.3. Charlson score was 1.7 and 1.5 respectively. Of the included patients, 1,665 were diagnosed with COVID-19 infection, and 2,769 were immunized with COVID-19 vaccine. There was no difference in the use of NSAIDS between the two periods (770 patients vs. 859 patients), but there was higher use of steroids in the COVID-19 period (83 patients vs 130 patients, p=0.04).

Conclusion: Based on this large population study, no association was found between COVID-19 infection and/or COVID-19 immunization and thyroiditis. However, higher use of steroids may suggest more severe disease during the COVID-19 period.

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COVID-19 vaccination and Graves' disease: a population based, matched case-control study

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Objective: Vaccination against coronavirus disease 2019 (COVID-19) an important component of coping with the pandemic. Anecdotal cases and case series reported an association between COVID-19 vaccination and the development of Graves' disease. We used data from Israel's largest health care organization to determine whether COVID-19 vaccination was associated with the incidence of Graves' disease.

Methods: We analyzed data from Clalit Health Services (CHS), which insures 4.7 million patients. A population-based, matched, case-control study was performed. Cases were defined as adult patients diagnosed with Graves' disease between December 2020 and November 2022. Each case was matched in a ratio of 1:2 with control based on age, gender, and autoimmune disease. Each control was assigned an index date which was identical to that of his/her matched case, which was defined as the date of Graves' disease diagnosis. Time between vaccination date and the diagnosis of Graves' disease/index date was assessed.

Results: A total of 726 patients with Graves' disease were matched with 1452 controls. The median age of the cohort was 40 (interquartile range, 30-53) years, and 25.5% (555/2178) were men. Similar proportions of study patients and controls have received the first, the second and the third dosage of COVID-19 vaccine. Positive test for COVID-19 was detected in 21.2% (154/726) of Graves' disease patients and 19.4% (282/1452) of controls (p=0.33). In a univariate analysis, first COVID-19 vaccine was not associated with the incidence of Graves' disease [odds ratio 95% confidence interval: 1.15 (0.92-1.43)]. The mean time between first COVID-19 vaccination and the diagnosis of Graves' disease for cases or index date for controls was not significantly different [275.69 days (standard deviation 144.37) for cases compared to 275.45 days (standard deviation 145.76) for controls].

Conclusions: We have found no association between COVID-19 vaccination and the incidence of Graves' disease. Our study adds data to the thyroid safety of COVID-19 vaccine.

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Glycerol Phenylbutyrate Treatment for Monocarboxylate Transporter 8 (MCT8) Deficiency

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Bachground: The transmembrane monocarboxylate trenasporter 8 (MCT8) facilitates the transport of thyroid hormones (TH). Mutations in the gene that encodes MCT8 (SLC16A2) leads to a syndrome characterized by global developmental delay, apparently as a result of a reduced TH transport during the intrauterine and postnatal periods of critical brain development. A typical TH impairment accompanies the syndrome, characterized by high T3, low T4 and normal to mildly-elevated TSH. Over the years, several thyromimetic drugs that bypass MCT8 were used, demonstrating improvement in thyroid hormone profile with minor changes in the neurocognitive functions. Recently, In vitro studies demonstrated that the chemical chaperone Phenylbutyrate (PB) restored mutant MCT8 function and increased intracellular content of T3 in a patient-derived cell model.

Methods: Two monozygotic twin boys aged 14.5 years with MCT8 deficiency due to the SLC16A2 mutation c.962 CT; P321L were treated with accelerating doses of Glycerol Phenylbutyrate (GPB). In vitro study with human-induced pluripotent stem cell that expressed the P321L mutation showed that PB rescued the reduced expression of the transporter, leading to a restoration of TH uptake.

Over 13 months of follow-up, TH and related compounds (sex-hormone binding protein [SHBG] and lipid profile) were recorded. Serum metabolites of GPB were measured as a safety measure by LC/MS. Vital signs and anthropometric measures were recorded and neuro-cognitive parameters were evaluated by repeated neurological examinations, Gross Motor Function Measure (GMFM-G88) and Bayley-III Social-Emotional and Adaptive Behavior Scale (ABAS-3).

Results: After 7.5 months of treatment, at the peak dosage of GPB, mean free T4 increased by 25% (from 0.64±0.03 to 0.80±0.04, p0.001), reaching a normal level in one patient. Although mean free T3 decreased by 25% (from 7.10±0.54 to 5.30±0.28, p=0.003), the nadir levels were still above the normal range. TSH, thyroglobulin and SHBG levels were not significantly changed. At high dosage of GPB, the patients experienced nausea and vomiting and liver transaminases were transiently increased up to 65 IU/L, leading to a cessation of therapy. TH levels off treatment were regressed to initial levels and partially recovered upon renewal of therapy. Only minor positive neuro-cognitive changes were observed during GPB treatment.

Conclusions: In the first report of GPB treatment in MCT8 deficiency we found an improved TH profile, with minor neuro-developmental changes. This proof-of-concept study should be extended to patients with various mutations and clinically milder forms of the disease, aiming at earlier age of intervention.

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The association between maternal TSH levels and pregnancy outcomes in hypothyroid women

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Background: Hypothyroidism affects 3-5% of all pregnant women. Overt maternal hypothyroidism is associated with risk to the maternal-fetal unit, while the impact of milder forms of hypothyroidism is still debated.

Aim: To evaluate the association between maternal TSH during pregnancy and pregnancy outcomes among women with hypothyroidism.

Methods: This was a retrospective cohort study of pregnant women in Clalit health services (CHS) with available TSH tests during pregnancy who delivered between 1/2012 and 7/2021 in Clalit hospitals. Women were classified as hypothyroid if they met any of the following criteria (1) Maximal TSH in pregnancy4, (2) prior diagnosis of hypothyroidism (ICD-9 code) or (3)dispensed levothyroxine during pregnancy. The non-hypothyroid group represented none of the above. Demographic, clinical, and laboratory data were extracted using the Clalit Research Data sharing platform powered by MDClone. A Quassi-Poisson regression model was used to assess the association between mean gestational TSH level pre- and perinatal complications experienced.

Results: In all, 224,518 deliveries (144,753 women, 230,271 newborns) met the inclusion criteria during the study period. Hypothyroid women were divided into four groups according to average gestational TSH: excellent control (≤2.5, n=7089), controlled (2.5- 4, n=10,008), uncontrolled (4 -10, n=7,326), severely uncontrolled (10, n=517). The reference group included 199,578 women. Women with severely uncontrolled hypothyroidism had the highest mean TSH in each trimester, highest rates of positive Anti-TPO antibodies and were treated with higher doses of levothyroxine. Among hypothyroid women, rates of preeclampsia and gestational diabetes mellitus (GDM) were higher in those with excellent control, controlled, and uncontrolled groups in comparison to the healthy reference group (P0.001). Off note, rates of preeclampsia and GDM were lower among poorly uncontrolled hypothyroid women. Rates of preterm delivery were higher among all the hypothyroid groups compared to the reference group, while birth weight was higher among the reference group.

In a model accounting for maternal age, newborn sex, ethnicity, fertility treatments, multiparity, history of reccurent pregnancy loss and socioeconomic level, the first three groups were associated with an increased risk for any complication (RR of 1.15, 1.16, 1.09 from excellent controlled to uncontrolled). The analysis did not indicate a significant risk for severaly uncontrolled group, probably due to insufficient power.

Conclusion: Hypothyroidism during pregnancy, even when TSH was perfectly controlled, was associated with elevated risk of preterm delivery, preeclampsia, and GDM. However, the severety of hypothyroidism was not found to be a predictor for pregnancy complications.

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Are Higher BMI and Worse Metabolic Parameters Associated with More Aggressive Differentiated Thyroid Cancer? A Retrospective Cohort Study

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Background

There is convincing evidence that excess body weight is associated with an increased risk for numerous cancer types, including differentiated thyroid cancer (DTC). Moreover, in some types of cancers (e.g., breast) there is an association between cancer aggressiveness and obesity. However, the data regarding this association among DTC patients are conflicting.

Aim

To evaluate the relationship between body mass index (BMI) and metabolic parameters and the aggressiveness of DTC in a surgical cohort.

Methods

We retrospectively evaluated consecutive patients following thyroid surgery (partial or total thyroidectomy), operated in our institution between December 2013 and January 2021, with final histology reporting DTC. Patients were divided into 3 groups based on their BMI: normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), and obese (≥ 30 kg/m2). Histological characteristics which represent intermediate or high risk according to the 2015 American Thyroid Association (ATA) guidelines were specifically evaluated. In addition, we scrutinized differences between groups regarding treatment modalities and follow-up data. We conducted logistic regression analysis to assess the association between BMI, fasting glucose, triglyceride, and triglyceride/high density lipoprotein (HDL) ratio as continuous variables and any of the following higher risk DTC features: Aggressive variants, macroscopic extra-thyroidal extension, vascular invasion, lateral neck lymph node (LN) metastases, LN largest diameter≥3 Cm, extra-nodal extension, and distal metastasis.

Results: 211 patients were included in the final study cohort: 66 (31.3%) with normal weight, 81 (38.4%) with overweight, and 64 (30.3%) with obesity. Median follow-up was 51 months (range 7-93). Patients with normal weight were younger than patients with overweight or obesity (mean± SD: 41.53±15.37, 52.64±16.26, 51.14±13.5, respectively, p0.001). Most patients in all 3 groups were women (75-85%, p=0.239). Unsurprisingly, metabolic parameters showed gradient when patients with normal weight were compared to patients with overweight and obesity (median [Q1-Q3]): fasting glucose 91 (86-99), 95 (90-102), and 99 (91-117), respectively, p=0.001; Triglycerides 95 (71-154), 118 (88-166) and 123 (93-215), respectively, p=0.014. No differences in histological features, ATA risk for recurrence, response to therapy, and treatment modalities were demonstrated between groups. Logistic regression analysis confirmed that worse metabolic parameters were not associated with higher risk to harbor more aggressive DTC.

Conclusions

In our study, we could not demonstrate any association between higher BMI and aggressiveness of DTC. Furthermore, worse metabolic parameters were not associated with more aggressive DTC. These data suggest that higher BMI and worse metabolic parameters should not change the clinical attitude toward patients with DTC.

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Foxl2 and Nr5a1 Regulation in Differentiating and Mature Gonadotrope Cells in the Anterior Pituitary

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The mammalian reproductive system is regulated by gonadotrope cells in the anterior pituitary gland. These cells produce and secrete the gonadotropin hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH), responsible for germ cell maturation. Gonadotrope differentiation in the developing pituitary is driven by several transcription factors (TFs), among them FOXL2 and SF-1 (encoded by FOXL2 and NR5A1, respectively). FOXL2 and SF-1 also support mature gonadotrope function, notably expression of FSHB which encodes the FSH β-subunit. Despite their essential role in gonadotropes, little is known about how these factors are regulated in the pituitary. Their only known regulators are in embryonic gonadal development where these TFs play a role in the development of the ovaries and testes. However, the main regulatory factors in the gonads are not expressed in the developing pituitary. We aim to find what regulates FOXL2 and NR5A1 in both differentiating and mature gonadotrope cells. We hypothesize that expression of both genes is activated by pituitary-specific factors and regulatory elements. This is supported by an earlier study reporting a gonadotrope-specific enhancer for the murine Nr5a1. Using published ATAC-seq data we have identified two new putative enhancers near the Foxl2 locus, one of which looks like a gonadotrope specific super-enhancer. Targeting dCas9-KRAB to this region reduced Foxl2 mRNA levels, indicating a functional role. This function is supported by the presence of annotated ChIP-seq binding of TFs that are expressed in differentiating pre-gonadotropes but not in the gonads. Both Foxl2 and Nr5a1 have adjacent divergent long non-coding RNAs (lncRNAs) that might also play a role in regulating their expression by various mechanisms. These lncRNAs are co-expressed in a tissue-specific manner and respond to the same stimulus as the protein coding genes. These results offer new candidates for the regulation of two genes crucial for human fertility.

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Mechanisms involved in the protective effect of carotenoids, polyphenols, and estradiol in human skin cells under mitochondrial oxidative stress.

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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 and of various phytonutrients on skin health. The aim of the current study was to examine the damage to dermal fibroblasts by such mitochondrially generated ROS, and to study the protective effects of estradiol, carotenoids and polyphenols. Rotenone, a complex I inhibitor, was used to cause mitochondrial dysfunction in human dermal fibroblasts and its effects on mitochondrial and cytosolic ROS levels, cell death, apoptosis, MMP1 and pro-collagen secretion were determined as markers of skin damage. Rotenone increased mitochondrial and cytosolic ROS followed by increased NFκB and AP-1 transcriptional activity, apoptotic cell death, and MMP1 secretion and decreased collagen secretion. Pretreatment with estradiol or with carotenoid rich tomato extract and rosemary extract reduced mitochondrial and cytosolic ROS levels and MMP1 secretion and increased cell number and collagen secretion. These effects can be partially explained by inhibiting caspase 3 activity and by cooperatively increasing ARE/Nrf2 activity, which leads to upregulation of antioxidant proteins such as

NQO-1 and Trxr1. This was accompanied by decreased expression of MAPK2/3 and decreased activity of NFκB and AP-1 transcriptional activities. To determine if activation of ARE/Nrf2 is the mechanism for cell protection, this transcription system was inhibited using ML385 and ochratoxin A (OTA). The inhibition of ARE/Nrf2 prevented the protective effects of estradiol and the phytonutrients from rotenone induced cell death, probably by diminishing their effect to reduce cytosolic ROS. This study indicates that phytonutrients and estradiol protect skin cells from damage caused by mitochondria generated ROS and thus, may delay skin aging and improve skin health.

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Single Cell Analysis of Postnatal Pituitary Stem Cell Differentiation to Gonadotropes

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The anterior pituitary is a major endocrine gland, which controls and coordinates physiological processes through production of hormones by specific cell populations. One such process, reproduction, is regulated by gonadotrope cells, responsible for synthesizing and secreting FSH and LH. In mice, the number of gonadotropes increases substantially soon after birth, seemingly arising at least in part from differentiation of postnatal pituitary stem cells (PSCs). However, little is known about the signals and mechanisms responsible for PSC differentiation along this lineage. We hypothesize that cell-type specific transcription factors (TFs) drive this cell differentiation through opening and activation of enhancer regulatory DNA. We are examining these processes utilizing single cell transcriptomic and epigenomic data of PSC-derived cells from neonatal mice. Our initial scRNA-seq data indicate distinct cell clusters, some of which have committed to this lineage and express gonadotrope-specific markers such as *Cga*, *Gnrhr*, *Foxl2* and *Nr5a1*. SCENIC analysis identified cluster-specific regulons, which include the driving TF and their potential targets, while Slingshot analysis allows prediction of the lineage trajectory in pseudotime. This approach revealed several pioneer TFs that might play a role in gonadotrope differentiation. One of these, NeuroD1, is predicted to activate *Nhlh2*, *Nr5a1*, *Cga* and *Gnrhr* and is highly expressed also in human fetal gonadotrope precursors. Furthermore, ATAC-seq shows a region of gonadotrope-specific open-chromatin upstream of *NeuroD1*, which is likely a transcriptional enhancer. Nhlh2 is also a pioneer factor and found in the *NeuroD1* regulon, while the *Nhlh2* regulon contains *Nr5a1*. Both TFs, Nhlh2 and Nr5a1, are essential for normal pituitary development and puberty onset. Elucidation of the mechanisms underlying postnatal gonadotrope differentiation will reveal the basis of the central control of reproduction while hopefully shedding light on novel causes for aberrant reproductive function and infertility.

A high-throughput screen reveals novel regulation of MKRN3 in GnRH secreting mouse neurons via the activin receptor pathway

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Introduction-Central precocious puberty(CPP) is often associated with loss-of-function mutations in Makorin Ring-Finger Protein3 (MKRN3). Moreover, hypothalamic-MKRN3 mRNA levels decrease before puberty, suggesting its inhibitory role on GnRH secretion and therefore in inhibition of puberty onset. Although this decrease is well established, the mechanisms that mediate MKRN3-downregulation 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-In order to find genes whose expression correlates with that of MKRN3, we analysed publicly available RNA datasets from brain samples of rats and mice, and rat mediobasal hypothalami through juvenile to adulthood transition. This might indicate factors that control MKRN3 expression, as well as commonly-regulated factors and downstream targets. To characterize a possible role for some of these factors in the regulation of Mkrn3, we over-expressed them in hypothalamic GnRH secreting neuronal cell line(GT1-7), and manipulated some of their downstream signaling pathways. To examine the role of Mkrn3 in these cells, we over expressed Mkrn3 tagged with GFP, and then performed mass spectrometry MS/MS analysis to identify the proteins that are differentially expressed. We also performed co-immunoprecipitation(CoIP) analysis followed by MS/MS to identify proteins that interact directly with Mkrn3.

Results-The bioinformatic screen identified ~300 differentially-expressed genes that are shared across the datasets examined, whose expression correlated with Mkrn3. One of these candidates is the Activin receptor type1C(Acvr1c) whose expression is negatively correlated with that of Mkrn3 along development. Over-expression of a constitutively active form of Acvr1c in GnRH GT1-7 neuronal cell line, led to a reduction in Mkrn3 mRNA levels. Furthermore, induction of the endogenous Acvr1c by either activinA or activinB, reduced Mkrn3 expression in these cells. ACVR1C signals through activation of the transcription factors SMAD2/3, which harbor putative binding sites on the MKRN3 promoter, and we found that knock-down of Smad2 in GT1-7 cells increased Mkrn3 expression. Furthermore, our initial MS/MS analysis after Mkrn3 overexpression indicates altered expression of over 200 proteins.

Conclusions-We have identified several potential regulators of Mkrn3 in hypothalamic GnRH neurons. Among the candidates arising from this screen, we suggest that Acvr1c-mediated pathway might downregulate Mkrn3 expression during development to allow puberty onset. Additional studies are required to confirm the effects of Mkrn3 on the proteins whose levels were seen to change following its over-expression which, together with findings from the CoIP, should shed light on downstream functions of Mkrn3 in these cells.

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The Role of Pigment Epithelium-Derived Factor in Folliculogenesis

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Folliculogenesis is the process of follicles assembly and growth. The entire process occurs along several cycles that require a tight dialogue between the oocyte and its surrounding granulosa cells (GCs) and is mediated by endocrine and paracrine factors. Our previous research focused on pigment epithelium-derived factor (PEDF), a secreted glycoprotein, known for its anti-angiogenic, anti-inflammatory, and anti-oxidative properties. The studies placed PEDF as an important player in the female reproductive tract, which could alleviate pathological conditions in the female reproductive system. PEDF is highly expressed in the ovary, in GCs, theca cells, and in oocytes. Our current aim was to determine whether PEDF is involved in the process of folliculogenesis. To accomplish that, we used mice follicles and human primary GCs (hpGCs); mice follicles were mechanically isolated and classified into three stage groups according to size, hpGCs were isolated from pre-ovulatory follicles of patients undergoing IVF. We focused on known players in folliculogenesis, namely, follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), vascular endothelial growth factor (VEGF), and aromatase. We followed the expression of PEDF and key factors and examined the direct interplays among them during folliculogenesis by qPCR analysis. First, we followed the changes of individual genes at various developmental stages of folliculogenesis in mouse follicles. PEDF was found to be abundantly expressed in large preovulatory follicles, yet, its cellular expression was stable all throughout follicular development. Unlike in other systems previously examined, PEDF was positively correlated with the expression of VEGF. Second, we focused on the direct interplay among PEDF, FSH, and AMH during the final stages of folliculogenesis, using hpGCs. We demonstrated a significant elevation in PEDF mRNA level (140%) at 24 hours of FSH stimulation. Up to date, all treatments that hpGCs were subjected to had an inhibitory effect on its expression. For the first time, we succeed in demonstrating a stimulatory effect on PEDF. Furthermore, following AMH stimulation, we detected a decrease in the level of PEDF mRNA (70%) at 4 hours of stimulation. Finally, stimulating hpGCs with PEDF caused a significant decrease in the level of AMH receptor (AMHR) mRNA (80%) at 4 hours of stimulation. Our findings provide evidence for PEDF involvement in folliculogenesis and place it as a pro-folliculogenesis player that interacts with the main participants in the process of follicle growth; however, the mechanism of this process is yet to be determined.

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TGFβ1 Role in Fine Balancing Ovulation

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The ovary, the female gonad, contains the oocyte reservoir, each protected and nourished by somatic granulosa cells (GCs) and theca cells (THC), comprising the follicle. Follicle-stimulating hormone (FSH) propagates the recruitment of follicles to the ovulatory pool where they embark on the process of dominant follicle selection. Ovulation is stimulated by luteinizing hormone (LH) and leads to the formation of a new endocrine gland, referred to as corpus luteum (CL). A variety of TGFβ family members regulate folliculogenesis, one of which is transforming growth factor-β1 (TGFβ1). TGFβ1's role is well documented in early folliculogenesis and CL regression but its precise role in ovulation remains unclear. TGFβ1 is negatively regulated by Vasorin (Vasn), a trans-membrane protein, shed upon cleavage to the extracellular space, trapping TGFβ1 thus attenuating its activity. We hypothesize that TGFβ1 acts as an upstream regulator of the FSH-LH axis. We set to elucidate TGFβ1 role by utilizing different transgenic mouse models. In one previously established model, Vasn is deleted exclusively in the GCs of growing follicles, resulting in higher availability of TGFβ1 (Vasn cKO mice). On the other hand, we established a TGFβR2

cKO mouse model, in which a genetic inhibition of TGFβ1 is achieved by specifically deleting TGFβR2 in GCs of growing follicles. We demonstrated that upon hormonal stimulation of Vasn cKO mice, the number of FSHR and LHR-expressing follicles is higher. Moreover, the number of mucified COCs is larger, agreeing with our previous demonstration of increased ovulation size. Turning off the "TGFβ1 switch", in the TGFβR2 cKO mouse model, the number of FSHR and LHR presenting follicles is reduced but surprisingly, ovulation size remains unchanged, suggesting a compensating mechanism. Assessing TGFβ1 over availability effect on ovarian vasculature, we show that augmenting TGFβ1 promotes faster stabilization of blood vessels around antral follicles prior to ovulation and in the forming CL. As a prerequisite to the stabilization of vessels, angiogenesis is suppressed in TGFβ1 over availability. Finally, we showed the presence of Vasn, the TGFβ1 inhibitor, in human follicular fluid samples. Furthermore, we are completing the transcriptomic analysis of GCs isolated by flow cytometry from both models at the time of FSHR and LHR activation using high throughput Bulk RNA sequencing. Overall, our findings place TGFβ1 as a positive upstream regulator of FSHR, thus augmenting the ovulatory response.

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Sirt-1 Activator for Treatment of Post-Menopausal Hepatic Steatosis

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Intro: Menopause leads to a deranged cardiometabolic risk-profile including hepatic steatosis. Even after controlling for age and other risk factors, post-menopausal women exhibit a 2.4-fold increased risk for the development of non-alcoholic fatty liver disease (NAFLD). Post-menopausal hormone replacement therapy is not suitable for all woman and there is an urgent unmet need for new therapeutics for this rapidly growing population. The nicotinamide adenine dinucleotide (NAD) dependent deacetylase, SIRT-1, has been shown to regulate hepatic lipid metabolism, with positive results for SIRT-1 activation in the treatment of diet or alcohol induced hepatic steatosis. The effects of SIRT-1 activation in the context of post-menopausal NAFLD have not been studied. To separate the effects of chronological aging we used young ovariectomized (OVX) mice to study effects of estrogen deficiency and pharmacologic SIRT-1 activation on liver fat and related genes. Methods: 9-week-old C57BL/6 J female mice were subjected to OVX or a SHAM procedure and fed a standard diet. 6-weeks post-surgery, OVX mice were divided randomly (n = 10 per group) to receive either the pharmacologic sirt-1 activator SRT3025 at 50 mg/kg·d or a vehicle control, administered daily by gavage for 6 weeks till sacrifice, when liver tissue was harvested. Liver was homogenized and triglyceride (TG) content measured with a calorimetric assay (Caymanchem; 10010303). SIRT-1 protein was quantified by western blot and gene expression quantified using Quantitative Real Time PCR. Results: OVX led to a doubling of mean liver TG content (26.5 vs 13.3 mg/dl/total protein; p=0.01 vs SHAM). SRT3025 treatment led to a significant reduction in hepatic SIRT-1 protein levels with complete normalization of liver TG (12.17 vs 26.5 mg/dl/total protein; p=0.01 vs OVX). Analysis of gene expression revealed that SRT3025 treatment led to significant changes in the expression of lipid metabolism regulating genes including the downregulation of fatty acid translocase (CD36), Fatty acid synthase (FAS) as well as the lipogenic transcription factor ChREBP (Mlxipl). Conclusions: Treatment with the pharmacologic SIRT-1 activator SRT3025 completely normalized liver steatosis indued by OVX. SIRT-1 activation should be further studied as a potential target for treatment and prevention of post-menopausal NAFLD.

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Drug-drug interactions between glucagon-like peptide 1 receptor agonists and oral medications: a systematic review

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Aims/hypothesis

Glucagon-like peptide 1 receptor agonists (GLP1RAs) are used for treatment of diabetes type 2 and obesity. One of their important mechanisms of action is slowing of gastric emptying, which might influence the absorption of oral medications. We aimed to review data on drug-drug interactions between various GLP1RAs and concomitantly administered oral drugs.

Methods

The PubMed and EMBASE databases were searched up to May 30, 2022. Data was extracted from pharmacokinetic studies and from product prescribing sheets reporting data without access to the original study. Only injectable GLP1RAs were included. Studies on oral GLP1RAs and studies on interactions between GLP1RAs and anti-hyperglycemic or injectable medications were excluded. Primary pharmacokinetic outcomes were the rate (Cmax, tmax) and extent (AUC) of absorption of the co-administered oral drug. Findings were synthesized and presented individually for each oral drug. The investigated drugs represent all classes in the Biopharmaceutics Classification System (classified by solubility and permeability).

Results

Twenty-one reports (exenatide=8, lixisenatide=2, liraglutide=5, dulaglutide=2, albiglutide=2, semaglutide=2, synthetic GLP1=one report) and data from six prescribing drug sheets were included. Most studies showed an overall low risk of bias. Administration of GLP1RAs resulted in unaffected or reduced Cmax and delayed tmax of drugs with high solubility and permeability (warfarin, combined contraceptive pills, acetaminophen), drugs with high solubility and low permeability (angiotensin converting enzyme inhibitors), drugs with low solubility and high permeability (statins) and drugs with low solubility and permeability (digoxin). However, in most cases the GLP1RAs did not affect the AUC of co-administered oral drugs or resulted in minor changes in the AUC that are not considered to be clinically significant. Pharmacodynamic studies did not show any difference in clinically relevant endpoints (INR for warfarin, gonadotropin levels for contraceptive pills, lipid profile for statins, BP for angiotensin converting enzyme inhibitors).

Conclusions/interpretation

The observed reduction in Cmax and delayed tmax of oral drugs co-administered with GLP1RAs are consistent with the known effect of delayed gastric output by the latter. Nevertheless, the overall drug exposure was generally unaffected or was not predicted to be clinically significant. This was further supported by unaffected pharmacodynamic measures. These reassuring results imply that dose adjustments are probably not needed for simultaneous use of GLP1RAs with oral medications. Still, these reassuring results should be carefully generalized to other medicinal products, especially when treating patients with background gastroparesis or kidney dysfunction, or when considering drugs with narrow therapeutic index.

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What causes Fasting Hyperglycemia in Pre-Diabetes?

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The early stage of type 2 diabetes is characterized by high insulin levels (hyperinsulinemia). Yet beta cells do not secrete enough insulin to maintain normal fasting blood glucose levels. It is generally hypothesized that hyperinsulinemia causes stress to the beta cells, prohibiting it from secreting sufficient insulin to normalize glucose levels.

The ability of the beta cell to sense glucose is a result of its unique metabolism. Glucose, but not other carbon sources such as pyruvate, lactate, and non-essential amino acid can enter the cell. Restriction of the pentose phosphate pathway and lactate secretion couples extracellular glucose with ATP synthesis. An increase in the cellular ATP/ADP ratio leads to depolarization of the beta cell and insulin secretion.

We modeled beta cell metabolism using flux balance analysis (FBA). This computational method considers key metabolic reactions in the cell, and enables monitoring the metabolism of sugars and amino acids in the cell under different conditions. The model demonstrates that when the demand for insulin synthesis is high, as in hyperinsulinemia, there is an increase in metabolic processes that utilize intermediates from the TCA cycle to synthesize amino acids, and consequently a decrease in the mitochondrial ATP production. As a result, higher levels of extracellular glucose are required to reach high ATP/ADP, leading to fasting hyperglycemia.

In conclusion, we propose that allocation of TCA intermediates into insulin synthesis rather than ATP production can disrupt accurate glucose sensing and result in fasting hyperglycemia.

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Mood and Personality Changes After Bariatric Surgery in Diabetes Patients

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Background: The prevalence of mental health disorders is reportedly higher in obese individuals as compared to controls. Studies have shown higher rates of depression, anxiety, low self-esteem, and impaired quality of life. The severity of these psychological conditions has been related to the degree of obesity. Bariatric surgery is presently the most effective treatment for morbid obesity. Studies have shown that the procedure of bariatric surgery does not only lead to substantial weight reduction but also improvements in physical as well as psychological status.

Most of the studies have examined the long-term implications of the surgery on various dimensions, and none has examined outcome after mini-gastric bypass. This study examined the short-term implications of the surgery on mood and personality in diabetic patients.

Methods: Fifteen patients (8 women, 7 men) between the ages of 21-65 years (Mean = 48.93, SD = 11.03) were evaluated before and 3-6 months after bariatric surgery (9 mini-gastric bypass, 3 Roux-en-Y gastric bypass and 3 laporoscopic sleeve gastrectomy) at the Institute of Endocrinology at the Tel Aviv Sourasky Medical Center. All the participants filled the State-Trait anxiety inventory (STAI), the Beck depression inventory II (BDI-II), and the Big Five Inventory (BFI). In addition, we examined different physical indices and cognitive performance using computerized cognitive battery, pre-post-surgery.

Results: We found a significant decrease in both depression and anxiety ($p = .025$, CI = [.59, 7.57]; $p = .005$, CI = [2.33, 10.73], respectively). Focusing on personality changes, a significant increase in extraversion trait was demonstrated ($p= .004$, CI = [-2.37, -.56]). In all these variables, larger changes were seen in women than in men.

Conclusions: The results suggest that after bariatric surgery patients experience significant psychological health improvements along with positive personality changes. These findings underscore favorable mental short-term of bariatric surgery. Such early changes should be identified to allow individually tailored adjustment of psychological and other modes of ancillary treatment. Furthermore, recognition and timely treatment adjustment in treatment early on after the surgery may lead to more stable and beneficial results in the long-term.

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The effect of hypokalemia during the treatment of diabetic ketoacidosis. A retrospective, single-center analysis

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Background: Patients with diabetic ketoacidosis (DKA) are potassium depleted and although routine treatment includes intravenous potassium, patients are prone to develop hypokalemia during the course of treatment. There is a concern that hypokalemia during DKA management can lead to severe adverse events including arrhythmias and sudden cardiac arrest. However, the actual effect of hypokalemia during DKA treatment on mortality has not been fully evaluated. In this study, we compared the outcomes of patients hospitalized due to DKA with or without hypokalemia.

Methods: Using MDClone©, we retrieved all the hospitalizations of adult patients (age over 18) with moderate or severe DKA (defined by a combination of a DKA clinical diagnosis noted in the electronic medical records, pH under 7.3, glucose 250 mg/dl and intravenous insulin administration) in Rambam Medical Center between 2/2012-1/2020. We compared demographic, anthropometric, and hospitalization variables and laboratory tests throughout admission, 30-day mortality, and total mortality between patients who did or did not develop hypokalemia.

Results: In the defined period, 456 hospitalizations with DKA filled all criteria and had no missing data. There were 304 hospitalizations (66.7%) with hypokalemia (Potassium 3.5 meq/L within the 3 days before or after the time of the lowest pH was measured) and 152 hospitalizations (33.3%) in which hypokalemia did not occur.

Compared to patients who did not develop hypokalemia, patients who developed hypokalemia were, on average, younger (46.3±19.3 vs 52.3±21.5years old, p=0.003), had a lower lowest pH during hospitalization (7.08±0.14 vs 7.15±0.11, p0.001), lower bicarbonate (8.99±4.50 vs 12.3±4.11, p0.001) and lower creatinine (0.88±0.88 vs 1.27±0.87, p0.001).

A significantly higher percentage of hospitalizations of patients who developed hypokalemia was in the ICU (36.8% vs 13.8%, p0.01), and hypokalemia during DKA treatment was associated with a longer hospital stay.

30-day mortality was similar among the patients with hypokalemia compared to those without hypokalemia (6.3% and 7.9% respectively, P = 0.55). The same was noticed considering long-term mortality until the day of analysis (26.6% and 33.6 % respectively, P=0.13).

Conclusions: Although hypokalemia occurs very commonly during treatment of moderate to severe DKA, it is not associated with a higher short or long-term mortality.

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Safety and efficacy of non-insulin therapy in hospitalized patients with type 2 diabetes mellitus – a systematic review and meta-analysis of randomized control trials

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Introduction:Clinical guidelines recommend insulin as the mainstay of therapy for hospitalized patients with diabetes mellitus. There is limited data on the safety and efficacy of non-insulin antihyperglycemic therapies in inpatients. The aim of the current study is to evaluate safety and efficacy of non-insulin anti-hyperglycemic therapy in hospitalized patients with type 2 diabetes mellitus (T2DM).

Methods:Systematic review and meta-analysis of randomized controlled trials (RCTs) examining treatment of hospitalized patients with T2DM with insulin vs non-insulin therapy. We searched PubMed and the Cochrane Library for RCTs published from inception to November 30, 2022. We also searched for ongoing trials in clinicaltrials.gov. Risk of bias was assessed using the Cochrane risk of bias 2 (ROB 2) tool. Primary outcomes were mortality within 30 days and hypoglycemic events during hospitalization. The current meta-analysis includes two parts, the first is a comparison between insulin and non-insulin therapy and the second is a comparison between insulin and a combination of insulin+non-insulin therapy.

Results:A total of 14 randomized control studies and 1570 patients were included. The two most studied medications were dipeptidyl dipeptidase 4 inhibitors (DPP4i) and Glucagon-like peptide 1 receptor agonists (GLP1-RA). There was a lower incidence of 30-day mortality in the insulin+non-insulin group compared with the insulin group without statistical significance, RR 0.64 (95% confidence interval (CI) 0.30-1.35, I2=0%). Hypoglycemic events were significantly lower with the non-insulin therapies compared to insulin therapy (RR 0.23 95% CI 0.09-0.55). Mean daily glucose levels were lower in the insulin group compared with the non-insulin group by 8.71 mg/dL (95% CI 2.04-15.38, I2=0%), but mean daily glucose levels were significantly lower in the insulin+non-insulin group compared to the insulin group, mean difference -10.83 mg/dL (95% CI -14.78-(-6.87), I2=20%). The most common side effects were gastrointestinal and were more prevalent in the non-insulin group. Serious side effects of non-insulin therapy were rare. The difference in hypoglycemic events was not significant when non-insulin+insulin treatment was compared with insulin, RR 0.75 (95% CI 0.52-1.09, I2=0%) in favor of the combination therapy.

Conclusions:Use of non-insulin therapies either with or without insulin, results in lower rates of hypoglycemia and smaller number of insulin injections compared with the traditionally recommended insulin treatment alone. Non-insulin in combination with insulin therapy is more effective than insulin alone in reducing blood glucose levels. Thus, use of non-insulin-based therapy, especially GLP1-RA and DPP4i, is safe and effective for control of hyperglycemia in hospitalized patients, and should be encouraged.

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The impact of chronobiological disorders on gestational diabetes mellitus outcomes: The Chrono-Nutrition Gestational Diabetes Study

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Background: Studies have shown that chronobiological factors may adversely impact glycemic control in patients with type 2 diabetes mellitus (T2DM). Data on the potential effect of chronobiological disorders on the course of gestational diabetes mellitus (GDM) and their relationship to pregnancy outcomes remain sparse.

Objective: To assess the association of chronobiological disorders with glycemic control and offspring birthweight in women with GDM.

Design: A prospective observational study was conducted. The cohort included women aged 18-45 years with a singleton pregnancy. They were randomly selected from among women undergoing follow-up for GDM at a Maternal-Fetal Medicine Unit of a tertiary medical center during 2016 and 2017. Nutrition, sleep, and lifestyle patterns were assessed from onset of GDM until birth along with glycemic control and obstetrical outcomes. Data were collected by a structured interview and from the medical files.

Results: Multivariate analyses were performed on a cohort of 208 women. Suboptimal glycemic control was associated with a late breakfast (RR=2.26; 95% CI 1.09-4.67). Any 10-gram increase in carbohydrate intake at evening increased the risk 1.19 times for suboptimal glycemic control (RR=1.19; 95% CI 1.003-1.42), and 2.14 times for poor sleep quality (RR=2.14; 95% CI 1.04-4.41). The adjusted relative risk for birthweight above the 85th percentile was associated with an excessive 10-gram increase of carbohydrate intake at morning (RR=1.70; 95%CI 1.30-2.23) and at evening (RR=1.39; 95%CI 1.16-1.67).

Conclusion: Chronobiological disorders are associated with a suboptimal glycemic control and large-for-gestational-age newborns in women with GDM.

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Monogenic Diabetes Multigene Panel Results in Patients Selected on Clinical Basis- far beyond the 7 genes….

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Background

Monogenic diabetes (MD) is a heterogenic group, caused by a single gene mutation in one of over 40 genes. Accounting for approximately 1-2% of all diabetes cases; diagnosis has been shown to improve management in approximately 50% of cases.

Our aim was to assess the genetic and clinical characteristics of an ethnically diverse cohort of patients suspected of MD on a clinical basis.

Methods

A retrospective cohort study on all patients referred to MD gene panel testing in our center, between 7/2021 and 12/2022. Referral was made on a basis of clinical suspicion of monogenic diabetes: young age at diagnosis, non-type 1 diabetes features, normal BMI, and a strong family history. Testing was performed by either Pronto lab, evaluating 26 gene panel, or by Clalit Genomic Center Lab -evaluating 117 genes.

Results

A total of 50, out of 63 referred patients, gave consent and were genetically tested. Of those 28 (56%) were females and 22 (44%) were males. Regarding ethnicity, 33 patients (66%) were Jewish and 17 (34%) were Bedouin Arabs. Mean age at diabetes diagnosis was 24 years (range, 10-40), average BMI (± standard deviation) was 26±4.8. Thirteen patients (13/50 ,26%) had a pathogenic or likely pathogenic (LP) variant in one of the panel genes: 4 patients- HNF1A, 3 patients- WFS1, and one patient in each of the following genes: GCK, HNF4A, CEL, BLK, INSR and PLIN1. Another 13/50 (26%) had a variant of unknown significance (VUS) in one or more of the panel genes. 24 (48%) had negative result. In the pathogenic/LP group, 12/13 (92%) were Jewish and only one (8%) was a Bedouin Arab. Interestingly, among patients with VUS results and those with negative results, 53% and 38% were Bedouin Arabs, respectively.

Conclusion

MD prevalence in patients selected on a clinical basis is high among non-Arabs. The high prevalence of VUS and negative results among Bedouin Arabs patients suggests a low yield of the current genetic panel in this population and calls for expanding the scope of diabetes genetic investigation to diverse populations.

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Israel National Wolfram Syndrome Registry

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Wolfram Syndrome type 1 (WFS1), or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), is a rare multi-systemic disease. It is caused by biallelic mutations in the WSF1 gene and is associated with a median lifespan of 30 years. A recently discovered probable founder mutation in the Ashkenazi Jewish population (c.1672CT, p.Arg558Cys) has a frequency of 1.34% and is associated with a relatively mild phenotype. A single case series, published in 2021 (PMID: 33763535), describes eight patients who are homozygous for this mutation, with diabetes mellitus (DM), bilateral optic atrophy and no hearing loss.

We report the launch of the first multi-institutional Israel Wolfram Registry, aiming to describe the natural progression of the disease to determine phenotype-genotype correlations in the Israeli population. We intend to assess the potential influence of environmental factors, medications and co-morbidities on disease progression.

Two hospitals are participating in the registry to date, Sheba and Soroka Medical Center. Since May 2021, 14 Jewish patients (5 males; 11 Ashkenazi and 3 mixed Ashkenazi and non-Ashkenazi) from 11 unrelated families signed consent and completed baseline assessments. At time of enrollment, age ranges from 14-71 years, with a mean of 35.1±17.2 years. Nine patients are homozygous for c.1672CT, and 5 are compound heterozygous (c.1672CT in combination with other pathogenic variants). Mean age of disease diagnosis is 29.8 years. Twelve patients have insulin-dependent DM, with a mean age of diagnosis 23.7±12.8 years, and a mean HbA1c of 7.0%±1.5%. DM was diagnosed on average 10 years before WFS1. Only one patient suffers from any known DM complications, in the form of coronary artery disease in advanced age. Seven patients are currently treated with liraglutide. Eleven have optic atrophy, with a mean age of diagnosis 24±11 years, an average of seven years before WFS1. While one patient is legally blind, all others retain functional vision. Seven patients endorse urological symptoms, with a mean age of onset 22±21 years. While two patients suffer from diabetes insipidus, and one from apparent central hypogonadism, there is no other evidence for pituitary deficiencies. One patient has partial sensorineural hearing loss. Additional institutions and patients have indicated interest in joining the registry, and recruitment is ongoing.

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Modeling the effects of maternal type 1 diabetes on embryonic development in mice

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Women with type 1 diabetes (T1D) suffer from higher rates of pregnancy complications. The risk of adverse pregnancy outcomes, including perinatal mortality, congenital malformations and preterm birth, is two to five-fold higher than the general population. Fetal macrosomia, in which newborns are large for their gestational age, is particularly a common problem, occurring in half of T1D pregnancies.

Poor glycemic control before and during pregnancy is related to congenital malformations and perinatal mortality, while fetal macrosomia is associated with high maternal glycated hemoglobin (HbA1c) levels. Nevertheless, women with T1D that maintain nearly optimal glycemic control still have an increased incidence of perinatal complications, including macrosomia. It remains unclear which factors other than glucose lead to an increased risk of macrosomia and how to improve pregnancy outcomes for T1D patients further.

To study factors causing fetal hyperinsulinemia and how maternal T1D affects embryonic development, we use the TET-DTA system to ablate beta cells and model pregnancy during T1D in female mice. Using this model, we show a bimodal effect of maternal hyperglycemia on fetal growth regulated by the fetal insulin-secreting beta cells. Moreover, we use this model to examine novel interventions to improve pregnancy outcomes, such as low-carb diets.

14:45-16:00 22.5 Parallel Session
Guided Poster Sessions - Hall B

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Increased Fracture Risk Among Children and Adolescents with Celiac Disease: A Nation Wide Cohort Study

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Background: One of the complications of celiac disease (CD) is decreased bone density. Our aim was to analyse the risk of fractures among children with CD compared with matched children without CD; and to identify clinical and laboratory risk factors to fractures among children with CD.

Methods: This registry-based cohort study included 2,372 children with CD and a large, matched comparison group of 11,860 children. Demographic and clinical data, anthropometric measurements and laboratory results were extracted from the electronic database of Meuhedet, a health maintenance organization. Fracture events at ages 1-18 years were identified by coded diagnoses.

Results: The overall fracture incidence rate was 256 per 10,000 patient-years (PY) in the CD group and 165 per 10,000 PY in the comparison group (p0.001). Among boys, the fracture incidence rates were 301 per 10,000 PY and 202 per 10,000 PY (p0.001), for the respective groups; and among girls 224 vs 138 per 10,000 PY, respectively (p0.001). The stratified hazard ratios (HR) to have a fracture was 1.57 (95%CI 1.43-1.73, p0.001); and for multiple fractures 1.67, (95%CI 1.38-2.01, p0.001). Analyse of the periods before and after the diagnosis of CD separately, showed that during the period until the diagnosis, the stratified HR for fractures among children with CD compared to children without celiac was 1.64 (95%CI 1.42-1.88, p0.001).

The stratified HR at the period from the diagnosis to the end of follow-up was 1.46 (95%CI 1.26-1.71, p0.001).

Conclusions: Children with CD had greater fracture risk than a matched group without CD both preceding and following the CD diagnosis.

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A single center experience with opportunistic diagnosis of osteoporosis by artificial intelligence-the time has come

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Background:

Osteoporosis (OP) is underdiagnosed and frequently left untreated. CT derived bone mineral density (BMD) and identification of vertebral compression fracture (VCF) on CT done for another indication are 2 new artificial intelligence (AI) based techniques for opportunistic diagnosis of OP. Our aim was to assess the clinical impact of opportunistic diagnosis of OP

Methods:

This retrospective study included men and women over age 50, insured by Clalit HMO, who underwent a CT scan for any reason at our institution and were identified by NanoxAI software as having a VCF in one or more vertebrae. Patients were excluded if a radiologist did not confirm the VCF, had a prior diagnosis of a motor vehicle accident (MVA), multiple myeloma, or spinal metastases. CT-derived BMD was calculated using Hounsfield units (HU) and when available results of DXA-BMD were retrieved. Demographic, clinical, and biochemical data including medication purchase were collected from the electronic medical records.

Results:

In a 4 months period, one hundred and fifty-one patients with VCF met the inclusion and exclusion criteria, of which only 71 (47%) had a prior diagnosis of osteoporosis. Of the 71 patients with prior diagnosis of OP only 12.7% purchased any OP medication in the 2 years prior to the index CT. Patients without a prior diagnosis of osteoporosis were younger (mean age 73.02 vs. 77.27; p=0.016) and had higher rates of male gender (58.8 vs. 26.8%; p0.001). Ethnicity and marital status were similar in both groups as were rates of prior diagnosis of diabetes mellitus and rheumatoid arthritis. Twenty-five-dihydroxy vitamin D levels were higher and alkaline. phosphate levels were lower in patients with a prior diagnosis of OP (69.25 vs. 53.29 nmol/L; p=0.038), and (101 vs. 78 U/L; p=0.025) respectively. Only 28% of the cohort underwent BMD-DXA scans in the 4 years prior to the index CT; T scores were significantly lower in the group with prior diagnosis of OP in spine (-0.29 vs. -2.22; p0.001), femur neck (-1.66 vs. -2.42; P=0.009) and total hip (-1.18 vs. -2.3; p=0.004). while CT derived BMD equivalents were similarly low in both groups with VCF irrespective of prior diagnosis of OP (95.05 vs. 90.33 HU p=0.540).

Conclusion

Our results highlight the underdiagnosis and the treatment gap in osteoporosis which was significantly higher in men. Routine opportunistic diagnosis of OP by AI is feasible and will contribute to improved diagnosis and treatment of OP.

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Normocalcemic primary hyperparathyroidism is an early stage of pimary hyperparathyroidism according to Fibroblast Growth Factor -23 level.

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Normocalcemic primary hyperparathyroidism is a variant of primary hyperparathyroidism with consistently normal albumin-adjusted or free-ionized calcium levels. It may be an early stage of classic primary hyperparathyroidism or could represent primary kidney or bone disorder characterized by permanent elevation of PTH level. Aim of the study The study aims to compare the FGF-23 levels in patients with PHPT, NPHPT, and normal calcium and PTH levels. Methods Our study included patients who were referred to the endocrinology clinic with a presumptive diagnosis of primary hyperparathyroidism, an isolated increased level of PTH, or reduced bone densitometry. For each patient, we performed blood analysis of FGF-23, calcium, phosphate, vitamin D [25(OH)D3], estimated glomerular filtration rate (eGFR), bone turnover markers, and urine analysis for calcium/creatinine ratio. Results Our study included 105 patients. Thirty patients with hypercalcemic hyperparathyroidism (HPHPT group), thirty patients with elevated PTH and normal calcium levels (NPHPT group), and 45 patients with normal calcium and PTH levels in the control group. FGF 23 level was 59.5± 23 pg/ml in the NPHPT group, 77±33 pg/ml in the HPHPT group, and 49.7±21.7 pg/ml in the control group (p=0.012). The phosphate level was lowest in the HPHPT group: 2.9 ±0.6 vs 3.5±0.44 in the NPHPT and 3.8±0.5 in the control groups (p=0.001). No differences were found in eGFR, 25(OH)D3, C-terminal telopeptide type I collagen (CTX) and procollagen type 1 N-terminal propeptide (P1NP) levels, and bone densitometry scores between the three study groups. Conclusion. Our findings suggest that NPHPT is an early stage of PHPT. Further studies are needed to determine the role of FGF-23 and its usefulness in NPHPT.

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Clinical and Molecular Characteristics and Long-term Follow-up of Children with Pseudohypoparathyroidism Type 1A.

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Context. Pseudohypoparathyroidism type IA (PHPIA) is a rare genetic disorder characterized by hormone resistance and a typical phenotype named Albright Hereditary Osteodystrophy. Unawareness of this rare disease leads to delays in diagnosis.

Objectives. The aims of this study were to describe the clinical and molecular characteristics of patients with genetically confirmed GNAS mutations and to evaluate their long-term outcomes.

Design. A retrospective search for all patients diagnosed with PHPIA in two referral centers in Israel was conducted.

Results. Nine children (eight females) belonging to six families were included in the study. Five patients had GNAS missense mutations, two had deletions and two had frameshift mutations. Four mutations were novel. Patients were referred at a mean age of 2.4 years due to congenital hypothyroidism (5 patients), short stature (2 patients) or obesity (2 patients), with a follow-up duration of up to 20 years. Early obesity was observed in the majority of patients. Elevated PTH was documented at a mean age of 3 years, however hypocalcemia became evident at a mean age of 5.9 years, about 3 years later. All subjects were diagnosed with mild to moderate mental retardation. Female adult height was very short and five females had primary or secondary amenorrhea.

Conclusions. Long-term follow-up of newborns with a combination of congenital hypothyroidism, early onset obesity and minor dysmorphic features associated with PHPIA is warranted and molecular analysis is recommended since the complete clinical phenotype may develop a long time after initial presentation.

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Teriparatide Treatment of osteoporosis in Solid Organ Transplant Recipients – a single-center experience

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Background

Osteoporosis and fractures are prevalent but underdiagnosed in solid organ transplant recipients. However, data on the efficacy and safety of anti-osteoporotic treatment in this population is limited, especially on the use of parathyroid hormone (PTH) analogues. There is only one randomized trial on the use of teriparatide in kidney transplant patients (6 month, 26 patients) and several case reports, none shows data about fractures. We sought to explore real-life single center experience with teriparatide treatment in a large cohort of solid organ transplant patients.

Methods

Retrospective review of electronic medical records of solid organ transplant recipients (kidney, lung, liver, heart) that were followed up in Rabin Medical Center since 2012. We collected data on efficacy of treatment (fractures, bone density) and safety (hypercalcemia, hypercalciuria, kidney function, graft rejection). Descriptive analysis was undertaken.

Results

Thirty eight patients were included (male, n=12; age 61.3 ± 11.6 years; kidney n=10, lung n=20, liver n=8). Teriparatide was given as first line anti-osteoporotic treatment in 14/38 cases. The median duration of teriparatide use was 22.8 months (range 3-24 months, 5 patients with ongoing treatment on date of data extraction). The average follow up since start of teriparatide was 6.8 years. Eighty nine percent of patients had a history of previous fracture and 82% had multiple fracture. During follow up only five patients experienced an osteoporotic fracture (one patient – humerus + vertebral fractures on treatment, 4 patients during the post-treatment period). Teriparatide treatment increased bone density in all areas: lumbar spine 0.906 to 1.016 gr/cm2 (p=0.01), left femoral neck 0.672 to 0.711 gr/cm2 (p=0.05), and left total hip 0.674 to

0.756 gr/cm2 (p=0.05). Five patients received teriparatide for less than 12 months. Only one patient developed hypercalcemia on treatment. No hypercalciuria was detected. Creatinine levels mildly increased (average 0.99 ± 0.3 to 1.15 ± 0.4, P0.05). There were no events of graft rejection on teriparatide therapy.

Conclusion

We present descriptive data on teriparatide use in the largest cohort of solid organ transplant patients to date. Teriparatide treatment increased bone density in transplant patients that were at very high risk for fracture. Only one patient suffered a fracture during therapy. No major adverse effects were detected. These results suggest that teriparatide may be an effective and safe treatment in transplant recipients.

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Parathyroid Hormone Levels Following Denosumab Therapy vs. Zoledronic Acid Therapy For Osteoporosis

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Background: Denosumab (DMAb) and zoledronic acid (ZA) are potent, anti-resorptive agents used to treat patients with osteoporosis. It has been suggested that they increase parathyroid hormone (PTH) levels in response to their antiresorptive effect, and that PTH elevation might be responsible for DMAb modeling actions on bone. The timeline and magnitude of PTH elevation post-DMAb and ZA has not been characterized in a large patient population.

Objective: To characterize PTH levels post-DMAb injection vs. baseline and vs. ZA infusion.

Material and Methods: Female osteoporotic patients, ≥50 years, treated with DMAb or ZA, 2008–2020 were included if PTH was 2mg/dl, vitamin D 50nmol/l or hyperparathyroidism. Post-injection PTH levels were linked time-wise to previous injections.

Results: A total of 35,375 women, ≥50 years received DMAb or ZA for the first time in 2008–2020; 26,341 met the exclusion criteria. Of the remaining women, 5,640 received a first DMAb injection and 3,394 ZA. The DMAb group was older (73.2 vs. 69.8 years), was treated more frequently with osteoporosis medications before the injection (56.5% vs. 50.3%) and more had sustained a fracture (15.8% vs. 13.9%) compared to the ZA group. Vitamin D level was 80.9±21.9 nmol/l. Repeat PTH was available for 2,206 DMAb patients and 1,444 ZA. Among 772 PTH measurements in the first month post-DMAb, it was 1.5ULN in 156 (20.1%) and 2.5ULN in 74 (5.1%), whereas among 807 PTH measurements 5-months post-injection, it was 1.5ULN in 112 (13.9%) and 2.5ULN in 9 (1.1%). One-month post-ZA, PTH was 1.5ULN in 35/169 (20.7%) and 2.5ULN in 11 (6.5%), and decreased to 1.5ULN in 23/213 (10.7%) and to 2.5ULN in 2/213 (0.9%), 5 months after injection.

Discussion: This is the first study to examine PTH levels in a large population receiving DMAb or ZA injections, with precisely-timed PTH measurements post-injection. PTH levels increased by 1.5ULN in 20% of osteoporotic patients who received DMAb or ZA, while it increased to 2.5ULN in ~5% post-injection. PTH levels declined gradually after treatment in both groups. It seems that PTH elevation is related to the antiresorptive effects of the drugs and is not a disease phenomenon. It is suggested to avoid checking PTH in the first few months post-DMAb and ZA therapy.

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The Variant Tyr 394Ser in the GCM2 Gene is Rare in a Cohort of Ashkenazi Jews with Primary Hyperparathyroidism

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Objective: Various genes have been associated with familial and sporadic Primary hyperparathyroidism, (PHPT) including activating mutations of the GCM2 p. gene. The aim of this study was to assess the prevalence of the GCM2 p. Tyr394Ser variant in the Jerusalem Ashkenazi Jewish (AJ) population with PHPT, and to conclude as to whether or not routine genetic testing is justified. Patients and Methods: the serum of 40 self-reported AJ patients with PHPT and 200 AJ controls was tested for the GCM2 p. Tyr394Ser variant. Demographic and medical information was extracted from the patient`s charts and evaluated accordingly. Results: two (5%) PHPT patients and three (1.5%) controls were heterozygotes for the tested variant. Our patients were mostly (87.5%) sporadic cases. One of the heterozygote patients had familial PHPT, the other had two parathyroid adenomas, and the levels of his blood and urinary calcium were extremely high Conclusion: Our results suggest that in AJ patients with sporadic single gland PHPT the likelihood of the tested variant is low and genetic testing is not justified.

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Compromised Adult Height In Females With Non-Classical Congenital Adrenal Hyperplasia Diagnosed In Childhood

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Introduction

Data on adult height (AHt) in individuals with non-classical congenital adrenal hyperplasia (NCCAH) are inconsistent.

Methods

We conducted a retrospective study of 109 females diagnosed with NCCAH at age 18 years who reached AHt. We studied AHt compared to target height (THt), and the correlation of AHt with clinical parameters.

Results

The mean age at diagnosis was 9.7±4.4 years, the mean follow-up was 10.9±6.3 years. Hydrocortisone treatment (11.0±5.0 mg/m2) was initiated at age 9.7±4.0 years. Bone age was more advanced in girls who presented with central precocious puberty or early puberty (CPP/EP) (n=43) than with timely puberty. AHt-SDS was lower than Ht-SDS at diagnosis (-0.8±1.0 vs. +0.2±1.3; P0.001), and -0.3 SDS shorter than THt (P0.001). Height, weight and BMI-SDS at last visits were similar between patients treated with glucocorticoids (n=92) and those never treated (n=17). AHt was comparable between patients with timely puberty and with CPP/EP, with no difference between those treated or not by GnRH analogue. AHt was similar between patients who were fully pubertal (Tanner 5), prepubertal (Tanner 1) and pubertal (Tanner 2-4) at diagnosis (158.0±7.6, 158.1±6.1 and 157.5±6.5, respectively; P=0.9). AHt-SDS was correlated with THt (R=0.67, P0.001) and Ht-SDS at diagnosis (R=0.7; P0.001), but not with age at diagnosis (R=-0.05, P=0.6), the extent of bone age advancement (R=-0.04, P=0.72), or glucocorticoid treatment duration (R=-0.11, P=0.34) or dose (R=-0.04, P=0.70).

Conclusion

AHt of females diagnosed with NCCAH in childhood was lower than their THt. Glucocorticoid treatment duration and dose, pubertal status at diagnosis, and having CPP or EP were not correlated with AHt.

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Cardiac biomarkers in Fabry disease exhibit distinct associations with cardiovascular outcomes: A (Rare) Prism for Cardiovascular Endocrinology

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Background: Fabry disease (FD) (OMIM 301500) is a rare x-linked metabolic disorder. Cardiovascular involvement in this rare metabolic disorder is common, including hypertrophy, fibrosis, heart failure and arrythmias. Troponin concentrations are often continuously elevated in FD patients, which at times may lead to false assumptions and unnecessary invasive investigations. Furthermore, while nt-proBNP, another cardiac biomarker, is regarded by some as a valuable biomarker in FD, its concentrations might be falsely high due to renal involvement in the disease. We sought to explore the associations between these cardiac biomarkers with myocardial architecture and clinical outcomes in patients with FD.
Hypothesis: Biomarkers in FD associate similarly with myocardial architecture and clinical outcomes.
Results: 107 patients from a tertiary referral center in the United Kingdom were included in this study. Mean age at first visit was 44.5+-17 years. Study population was composed of 40 males and 67 females. Twenty males and 43 females carried a classic mutation. At baseline, 27% had elevated troponin concentrations and 30% of patients had elevated nt-proBNP concentrations. Throughout follow-up, 17 cardiac-related hospitalizations were recorded, and 12 cardiac-related deaths occurred.
While troponin and nt-proBNP concentrations at baseline were closely related (r= 0.5, p 0.05), distinct associations with future occurrence of cardiac architecture pathologies were noted: elevated troponin concentrations associated with presence of late gadolinium enhancement and left ventricular hypertrophy in a statistically significant manner (late gadolinium enhancement: r=0.54, p0.05; hypertrophy: r-0.45, p0.05), but nt-proBNP did not. However, both biomarkers associated with adverse clinical outcomes, and nt-proBNP displayed stronger correlation with future heart failure events than troponin (r= 0.52, p
Conclusions:
Cardiac biomarkers associate differently with myocardial architecture pathologies, but similarly with clinical outcomes in FD. Our results imply distinct roles for troponin and nt-proBNP in adverse cardiac events in FD.

Non Interventional Weight Changes Are Associated With Alterations In Lipid Profile And In Triglyceride To HDL-Cholesterol Ratio

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Background and aims

Obesity is associated with dyslipidemia through insulin resistance and adipokines secretion, and weight loss can improve obese patients` lipid profile. Here we aimed to assess whether non interventional weight changes are associated with alterations in the lipid profile, particularly the triglycerides (TG) to high density lipoprotein (HDL) cholesterol ratio (TG/HDL) which is an emerging marker for insulin resistance, the metabolic syndrome and an elevated risk for coronary artery disease.

Methods

This is a retrospective analysis of subjects referred to annual medical screening. BMI, low density lipoprotein (LDL)- cholesterol, TG and HDL levels were measured annually. Patients were divided according to the change in BMI between visits: reduction of 5% ("large reduction"), reduction of 2.5-5% ("moderate reduction"), reduction of 2.5% or elevation of 2.5% ("unchanged"), elevation of 2.5-5% ("moderate increase") and elevation of 5% ("large increase"). The primary outcomes were the change in LDL, TG, HDL and TG/HDLbetween visits.

Results

The final analysis included 18,828 subjects. Mean changes in LDL (mg/dL), TG (mg/dL), HDL (mg/dL) and TG/HDL (%) were associated with BMI changes and were -3.89, -11.00, +5.76, -13.20 for “large reduction” BMI group, -0.96, -0.91, +2.99, -1.71 for “moderate reduction” BMI group, +1.30, +5.36, +1.93, +5.26 for “unchanged” BMI group, +2.91, +12.50, +1.30, +13.00 for “moderate increase” BMI group, and +3.91, +17.70, +0.43, +19.70 for “large increase” BMI group, respectively (p .01). The proportion of patients with 10% rise in TG/HDL progressively increased with the relative change in BMI (20.6%, 30.2%, 37.5%, 46.2%, and 50.2% for "large reduction”, “moderate reduction”, “unchanged”, “moderate increase”, and “large increase” groups, respectively, p .01). Compared to the “unchanged” group, the odds ratio for TG/HDL rise of 10% was 0.43, 0.72, 1.43 and 1.68 for "large reduction”, “moderate reduction”, “moderate increase”, and “large increase” groups, respectively
(p .01). Subgroups analysis by gender, initial TG/HDL and initial BMI revealed that the trends of TG/HDL change by BMI did not change significantly, albeit the association of TG/HDL by BMI was mildly mitigated in females.

Conclusions

Non-interventional weight changes, even modest, are associated with alterations in lipid profile.

Adipose Tissue Support Of Cancer Growth Is Mediated By The Adipokine FABP4

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Adipose tissue provides stromal support for tumor growth in many types of cancers by various secreted factors. Furthermore, adipose tissue dysfunction in obesity is an established risk factor not only for cardio-metabolic abnormalities, but also, as becoming increasingly evident, for increased cancer incidence and aggressiveness. Rapidly accumulating evidence suggest that the adipokine fatty acid binding protein 4 (FABP4), is an important facilitator of cancer growth and metastasis in various cancers.

Aim: As the obesity-attributable cancer burden is likely to continue and rise, identifying FABP4 as a stromal secreted factor that promotes tumor growth represents an attractive target for pharmacological interventions in obesity-related cancers.

Methods: We focused on two cancers that heavily depend on adipose tissue stromal support: pancreatic ductal adenocarcinoma (PDAC) that its incidence and pathogenesis are linked to obesity, and melanoma, for which the abundant adjacent sub-cutaneous adipose tissue provides key stromal support.

Results: Both melanoma and PDAC cells proliferation and migration are markedly enhanced in-vitro by incubation with mouse adipose tissue condition medium, effects that are significantly inhibited when adipose tissue of Fabp4 knockout (Fabp4-/-) mice is used. Furthermore, the in-vivo growth of melanoma or PDAC tumors is profoundly attenuated in Fabp4-/- compared to wild-type mice. Furthermore, neutralization of circulating FABP4 by monoclonal antibody inhibits in-vivo melanoma growth, which is comparable to the inhibition observed in Fabp4-/- mice. We applied unbiased approaches to elucidate FABP4 mechanism of tumor support. RNA-seq analysis suggests an immune-modulatory role for FABP4 in suppressing antigen presentation by cancer cells, decreasing cytokine signaling and PTEN activation. Lipid screening revealed alterations in lipid products of mitochondrial phosphatidylserine decarboxylase (PISD), implicated in anti-cancer phenotype.

Conclusions: Our preliminary results suggest that FABP4 provides a key stromal support to various tumors, thus highlighting this adipokine as an attractive anti cancerous therapeutic target.

Association between Body Mass Index, Thyroid Cancer, and Weight Change: A Longitudinal Follow-Up Study.

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Introduction: The incidence of thyroid cancer (TC) has appreciably increased over the last few decades, and it has become the third most common malignancy in young women.

Parallel growth in the prevalence of obesity and TC incidence suggests a potential role of obesity in thyroid carcinogenesis. Additionally, weight gain is a common complaint among TC patients after thyroidectomy. However, longitudinal studies on the association between BMI, TC, and weight change are scarce.

Aims: 1. To investigate the association between BMI and the occurrence of TC in Israeli young women. 2. To evaluate short- and long-term weight gain in TC survivors compared to healthy age-matched controls. 3. To identify independent variables associated with a higher basal BMI and increased weight gain in TC patients.

Methods: The Clalit-Health-Medical-Organization database was used to retrieve demographic and clinical data on 1309 women diagnosed with TC at age ≤40 years in the years 2000-2020, and 5247 age-matched healthy control women adjusted for calendar time at TC diagnosis. BMI and body-weight data were collected and compared between the groups at the time of diagnosis, as well as at several subsequent time points during a median follow-up of 10 years.

Results: Median age at diagnosis was 31.6 years (IQR 26.7, 35.4). Overall, 1169/1309 (89.3%) TC patients were treated with Levothyroxine. BMI in TC patients at the time of diagnosis was significantly higher than in controls (median 23.6/22.9 kg/m2, P0.001). Regression analysis showed that a higher basal BMI was independently associated with a TC diagnosis, an older age at diagnosis, and a lower socioeconomic status (SES). Weight gain was comparable between TC patients and controls throughout the follow-up. The following median values of weight gain were retrieved in TC patients and controls, respectively: 0-1 year post-diagnosis 0.6/0.5 kg (p=0.513), 1-2 years post-diagnosis 1.0/2.0 kg (p=0.807), 2-3 years post-diagnosis 2.4/2.0 kg (p=0.533) 3-4 years post-diagnosis 3.0/2.0 kg (p=0.408), last follow-up 2.1/1.7 kg (p=0.567). Higher weight gain during follow-up was associated with longer surveillance, older age at diagnosis, lower SES, and parity, and was negatively associated with a higher basal BMI.

Conclusions: Our study implies that the growing incidence of TC may be pathogenically linked to the spread of obesity. Nevertheless, the finding of a modest weight gain in TC survivors during a prolonged follow-up is reassuring and undermines the common patients` perception of weight gain. These results may aid healthcare providers in addressing weight concerns in TC survivors.

Microscopic Calcifications Isolated from Thyroid Nodule Fine Needle Aspiration Can Serve as Biomarkers of Thyroid Nodule Malignancy- A Proof of Concept Study

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Background

A major limitation of the current diagnostic approach of thyroid nodules (TN), which relies on ultrasound guided fine needle aspiration (FNA) for cytology (FNAC), is the high rate of indeterminate results (~30%). As punctate calcifications detected within a TN by neck ultrasound are considered a high-risk feature for thyroid cancer (TC), we hypothesized that the remaining material at the end of FNA procedures contains microscopic calcifications (MCs). We speculated that chemical analysis of MCs for elemental composition and morphology may differentiate malignant from benign TNs.

Methods

In this single-center study, samples were collected between 11/2020 and 12/2022 during routine FNAC procedures. Clinical decisions were made according to the accepted guidelines based on ultrasound and cytology. TN were labeled as malignant/neoplastic (TC or Non-invasive follicular thyroid neoplasm with papillary-like nuclear features [NIFTP]) based on final histology, or as benign using strict criteria including ultrasound characteristics, cytology, molecular testing, and final histology. We used a straightforward protocol for MCs isolation. Chemical analysis of MCs was based on scanning electron microscopy. Comparisons between final diagnosis of a TN being malignant/neoplastic or benign and the results of the compositional and morphological MCs analyses were conducted retrospectively.

Results

Samples from 124 patients were sent for chemical analysis in parallel with the routine cytological evaluation. Samples from 26 patients were used for protocol development, and 35 patients are still under clinical evaluation lacking final diagnosis. The remaining 63 patients underwent full clinical evaluation, and the residual FNA material was subjected to the MCs isolation protocol. In 52/63 patients (82.5%), MCs were identified. Interestingly, all 11 patients without identifiable MCs had final diagnosis of benign TNs. The final study cohort included 30 patients with benign TNs (median age: 54 years [range: 26-76 years], 83.3% females), and 22 patients with malignant/neoplastic TNs (median age: 42 years [range: 18-80 years], 63.6% females). Final histology was papillary thyroid carcinoma in 20 patients, one patient had NIFTP, and one minimally invasive follicular thyroid carcinoma. Morphologically, while MCs from patients with malignant/neoplastic TNs were spherical, MCs from benign TNs were crystals with sharp edges. Regarding elemental composition, zinc was present in 91% and 7% of MCs obtained from patients with final diagnosis of TC/NIFTP and benign TN, respectively (p0.001).

Conclusion

The presence of zinc within MCs isolated from FNAC residual material, together with MCs morphology can offer value as a biomarker for TC, increasing the diagnostic yield of the FNAC procedure.

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Long-term metabolic outcomes in Graves` disease: Is there a difference between oral anti-thyroid medications and radioactive iodine treatment?

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Introduction: The treatment of hyperthyroidism in patients with Graves' disease (GD) is associated with various metabolic comorbidities, including weight gain andan increased risk of cardiovascular and cerebrovascular diseases. Few studies have assessed the potential differences in metabolic outcomes between radioactive iodine (RAI) and oral anti-thyroid drug (ATD) therapies.

Aim: We sought to investigate the long-term (10 years) metabolic effects of RAI versus ATD therapy in GD. We also compared the occurrence rates following long-term use to those with short-term (5 years) use in order to explore a potential "legacy effect".

Hypothesis: RAI and oral ATD treatment will differ in their associated risk ofmetabolic sequelae, including the occurrence of hypertension, dyslipidemia, obesity,and diabetes.

Methods: Patients attending the Institute of Endocrinology at the Tel Aviv SouraskyMedical Center filled in a questionnaire on post-RAI or post-ATD treatment for GD.

Results: In total, 143 participants had been followed-up for 5 years, and 87 of them (age range 31-88 years, 65 females [74.7%]) had completed 10 years of follow-up(mean follow-up period 14±1 years). During the initial 5-year follow-up period, RAI treatment was associated with a significantly increased rate of obesity anddyslipidemia in the short-term, but no comparable differences persisted into the 10-year follow-up period. However, mean fasting glucose concentrations were higher among RAI recipients compared to ATD recipients (106 and 91 mg/dL, respectively, p=0.037) even after 10 years, and the mean triglyceride concentration was also higher in the former (127 and 88 mg/dL, respectively, p=0.02). There were no significant group differences in the rates of diabetes mellitus or dyslipidemia in the 10-year follow-up period.

Conclusions: RAI therapy is associated with long-term higher glucose and triglyceride levels compered to ATD therapy in patients with GD. Clinical metabolic diagnosis are comparable. The significant group differences in the occurrence of metabolic morbidities that had been observed after the first 5 years of follow-up persisted to a greater or lesser extent into the extended 10-year follow-up period, as evidenced by fasting glucose and triglycerides concentrations

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Serological Profile in Rheumatoid Arthritis and its Interplay with Autoimmune Thyroid Diseases

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Objective: Autoimmune thyroid diseases (AITD) are the most common organ-specific autoimmune disorders, with an estimated prevalence of 5%. AITD encompass the clinical scope of Hashimoto`s thyroiditis (HT) and Graves`s disease (GD). Rheumatoid arthritis (RA) is a relatively common non-organ-specific autoimmune disease with an estimated global prevalence of 0.5-1%. Numerous studies have investigated the association of thyroid disorders and RA in various populations, but results were inconsistent.

This study is aimed to assess the rate of AITD in RA patients and to further investigate these rates in subgroups of patients with seronegative RA, seropositive RA and dual-positive RA antibodies [i.e., positive anti-cyclic citrullinated peptide (CCP) and rheumatoid factor (RF)].

Methods: We used a big-data platform (MDClone Ltd., Israel) to create a cohort of RA patients with and without coexistent AITD. The cohort included 1316 patients who were treated in the Tel Aviv Sourasky Medical Center for any diagnosis between January 2008 and December 2022.

Results: The cohort consisted of 340 men (25.8%) and 976 (74.2%) women. The mean age at time of first RA coding in our referral center was 62.5±15 years. AITD was found in 15.5% of the entire RA cohort. Hypothyroidism was the most common thyroid-associated diagnosis (in 95.8% of patients with RA and AITD). When RA patients were further sub-classified to seronegative, seropositive and dual-positive RA, the rates of AITD were 11.8%, 17.6% and 25%, respectively (p=0.007). AITD rates in seropositive women and men were 20.6% and 8%, respectively (p0.001). In the RA-seronegative subgroup, the rate of AITD was 15.6% in women and 2.7% in men (p0.001). The mortality rates in RA-seronegative patients, RA-seronegative patients with AITD, RA-seropositive patients and RA-seropositive patients with AITD were 5.5%, 8.3%, 21.6% and 29.5%, respectively (p=0.05).

Conclusion: Our findings suggest that the prevalence of AITD in patients with RA is associated with the specific serological profile, with highest rates in RA patients who are positive for both anti-CCP and RF. Randomized prospective studies are required in order to explore any cause-and-effect correlation and to delineate the impact of AITD on RA outcome and mortality rates.

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Immune checkpoint inhibitors and severe insulinopenic diabetes mellitus: a single center experience

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Introduction: Severe insulinopenic diabetes (SID) is a rare complication of treatment with immune checkpoint inhibitors (ICPI). We describe herein the clinical characteristics, natural history and potential predictors of SID in cancer patients treated with ICPI.

Methods: We identified and retrospectively retrieved pertinent clinical data of all patients who presented with new onset SID following treatment with ICPI between October 2015 and December 2022 at the Tel Aviv-Sourasky Medical Center.

Results: 1621 patients were treated with ICPIs, of whom 13 (0.8%) patients developed SID. Seven were males (53.8%). Median age at diagnosis was 67 (IQR 60.5-77) years. Eight patients (61.5%) were treated with PD-L1 inhibitors, 3 (23.1%) with PD-1 inhibitors and 2 (15.4%) with a combination of PD1 and CTLA4 inhibitors . Two patients had a prior diagnosis of type 2 diabetes treated with oral medications while 2 other patients had a prior diagnosis of impaired fasting glucose. Three patients (23.1%) developed a concomitant thyroid dysfunction under ICPI. Median time from the initiation of ICPI to presentation of SID was 4 months (IQR 1-9). Five of the patients presented with SID within a month from exposure (38.5%). DKA was the presenting symptom in eleven patients (84.6%), 3 of which were treated with a SGLT2i . One patient (7.7%) died within one week of DKA presentation.

Conclusions: This is one of the largest single center series describing the onset and characteristics of SID following ICPI treatment .

This cohort emphasizes the importance of patient education and awareness for this potentially life-threatening complication. Better characterization of ICPI-induced diabetes will improve patient care and enhance our understanding of immune-mediated diabetes.

Age (Years)	Gender	Medication	Prior DM	DKA	Time between exposure and presentation (months)	Underlying malignancy	Concomitant Thyroid dysfunction
82	M	Nivolumab	DM2	+	13	HL	None
74	M	Avelumab	-	-	8	RCC	Hyperthyroidism
58	M	Pembrolizumab	-	+	4	MELANOMA	None
70	F	Pembrolizumab	DM2	+	4	Gastric Adeno CA	None
62	F	Nivolumab	IFG	+	29	Adeno CA Lung	None
66	F	Pembrolizumab	-	+	1	Ovarian Adeno CA	None
82	F	Pembrolizumab	-	+	1	Gastric Adeno CA	None
61	F	Pembrolizumab	-	+	9	Skin SCC	Hypothyroidism
67	M	Durvalumab	-	+	1	NSCLC	Hyperthyroidism
57	F	Ipilimumab+Opdivo	-	+	1	MELANOMA	Unknown
78	M	ipilimumab+Nivolumab	-	+	1	MELANOMA	None
76	M	Nivolumab	IFG	-	9	RCC	None
60	M	Pembrolizumab	-	+	4	Head and Neck SCC	None

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LMF1 *Associated* Chylomicronemia Syndrome

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Introduction:

Familial Chylomicronemia-FC syndrome is characterized by severely elevated triglyceride levels, i.e., levels of TG above 1000 mg/dl. Monogenic etiology is associated with a small but a significant fraction of Familial Chylomicronemia (FC) Syndrome cases, which is mainly attributed to a few genes, that are involved in Lipoprotein Lipase activity (LPL / LMF1 / APOC2 / GPIHBP1 / APOA5). Bi-allelic variants in these genes cause this rare Autosomal Recessive disorder with a prevalence of ~1 to a million. We herein report a case of a 51year old male, diagnosed with FC syndrome due to a homozygous pathogenic variant in the LMF1 gene, and the clinical implications of this diagnosis.

Case description:

A 51 years old male of consanguineous Jewish Yemenite ancestry, has been investigated in the Endocrinology Clinic due to recurrent pancreatitis. He was diagnosed with severe hypertriglyceridemia (TG levels up to 2300 mg/dl). His past medical history includes type 2 diabetes mellitus and complex PTSD. No family history could be retrieved.

Initial treatment included a combination of fibrates, statin, ezetimibe and omega3 fatty acids. The patient was instructed to avoid alcohol, and a strict dietary-fat restriction. Despite good adherence to this treatment, triglyceride levels remained high, around 700mg/dl, and he continues to suffer from mild episodes of pancreatitis that reduce his quality of life.

Molecular investigation:

Homozygous LMF1 c.1391GA p.Trp464* (RefSeq NM_022773), classified as "Pathogenic" according to the ACMG guidelines.

Discussion:

Involvement of LMF1 gene by loss-of-function mechanism has been initially reported in 2007 [Péterfy et al]. LMF1 gene encodes a transmembrane protein, which is involved in the maturation of lipoprotein lipase (LPL) and hepatic lipase in the endoplasmic reticulum. The LMF1 variant diagnosed in our patient, was previously described (doi: 10.1210/jc.2009-0594). Functional analysis of this variant revealed significantly reduced expression and activity of LMF1 protein.

The clinical presentation of our patient is consistent with the molecular diagnosis of Lipase Deficiency (OMIM #246650). Due to lack of improvement on current available treatments, he is a candidate for treatment with Volanesorsen-, a second-generation 2′-O-methoxyethyl (2′-MOE) chimeric antisense therapeutic oligonucleotide, that decreases plasma apolipoprotein C3 and triglycerides (TG) levels through LPL-independent pathways.

We suspect that the rarity of this syndrome is partly due to underdiagnosis, and the availability of Next generation sequencing will improve our diagnosis and treatment options for our patients. Our hope is to offer personalized treatment based on the specific molecular diagnosis.

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Differentiation of Gastric Corpus Enteroendocrine Cells (gEEC), Including L Cells

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gEECs play important roles in regulating digestion and satiety, but information on their development and homeostasis is limited. Stem cell populations, cell lineages, signaling pathways, and TF required for differentiation are poorly defined. Genetic tools in stomach research are lacking, and adult gastric organoids do not reliably generate gEECs or HCL-secreting parietal cells. These limitations impede our understanding of these cell types` function and development in reflux, gastric acidity, obesity, and gastric neuroendocrine tumors (NETs).

Our lab conducted scRNAseq experiments on human gastric corpus biopsies, including those from Post-Sleeve-Gastrectomy patients. The data identifies gEEC progenitors and mature cells and allows to map TFs and signaling pathways along gEEC differentiation. Similarly to intestinal EECs, Notch-inhibition is involved in early differentiation of gEECs, however, these cells are generally NGN3-independent. Ptf1a, another bHlH TF, is surprisingly expressed in gEECs, especially in ECLs. It’s considered a key TF in the development and maintenance of the exocrine pancreas while its role in EEC development was never addressed. Lineage tracing experiments using PTF1a-CreER mice have demonstrated PTF1a expression in progenitors to all gEEC types and a long cell lifespan of at least several months. Further Immunofluorescent experiments confirmed its expression also in human biopsies, and showed a change in protein localization inside the cell correspondent to cell maturation. ScRNAseq and histological studies performed on human biopsies revealed a significant increase in the proportions of ECLs at the expense of the hunger-hormone-secreting X cells following Sleeve-Gastrectomy. This shift is associated with upregulation of PTF1a and its exocrine target genes in ECLs. Furthermore, KO of PTF1a showed a complete elimination of ECLs at P1 mice, while other gEEC populations remained. This suggests a crucial role of PTF1a in ECL development and expansion after Sleeve-Gastrectomy and a neglectable involvement in differentiation of other gEECs.

The scRNAseq data also identified rare L cells in the human corpus, as well as GLP1R+ gEECs. These L cells express GCG, PYY, SGLT1 and PCSK1 but not PCSK2, thus allowing GLP1 synthesis. We confirmed Their existence using immunofluorescent methods on human and murine biopsies and we plan to better characterize their development and neuronal-connectivity using similar tools. We have also utilized murine and human-derived gastric organoids in order to study gEEC and L cell development. Specifically, we are attempting to expand these cell types in vitro by introducing relevant signaling molecules and expressing ectopic TFs via AAVs.

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Novel Cis-Regulatory Mechanisms of *Lhb* Transcription by Non-Coding RNAs and Non-Canonical DNA Structures

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Expression of the luteinizing hormone *Lhb* gene was shown previously to be directed by synergistic actions of lineage-specific transcription factors at conserved regions of the proximal promoter. However more recent extensive genomic analysis has expanded the repertoire of factors we now know to be involved in transcriptional regulation, revealing roles for distal transcriptional enhancers and long non-coding RNAs (lncRNAs), whose modes of action are only beginning to be elucidated. It has also become evident that regulatory regions of the genome are enriched with non-canonical DNA structures which bind various regulatory proteins, though their precise function and how they affect transcription are unclear. These structures include G-quadruplexes (G4s) which form on guanine-rich stretches of single-stranded DNA and iMotifs (iMs) on the complementary strand. We thus hypothesized that some of these more distal cis-acting elements might regulate the expression of *Lhb*. We identified in murine pituitary scATAC-seq data, a region of gonadotrope-specific open chromatin upstream of the *Lhb* gene, and chromatin conformation capture (3C) in murine gonadotrope cell lines confirmed that this distal region is in physical proximity to the *Lhb* promoter. We show that this region is enriched with H3K4me1, and transcribed to two bi-directional non-coding enhancer RNAs (eRNAs), both characteristic of transcriptional enhancers. One of the eRNAs was found to direct open chromatin at the *Lhb* promoter and is required for *Lhb* transcription, while guide RNA-mediated recruitment of dCas9- KRAB or dCas9-VP64 to this locus altered *Lhb* mRNA levels accordingly, confirming its functional enhancer activity. However, this enhancer activity is not sufficient, and splicing of an adjacent lncRNA is also required. This lncRNA increased *Lhb* expression when overexpressed in cis, and mutation of the U1 snRNA binding sites reduced *Lhb* expression dramatically. Several sequences in this regulatory region can form G4s and/or iMs, including at the central region of the enhancer, which was confirmed by circular dichroism and ChIP. These various structures have distinct effects on transcription and are affected differentially by local conditions including changes in pH or hormonal treatments. HMGB2, which is known to bind structured DNA, was found to bind the enhancer iM in cells and in vitro. HMGB2 knockdown reduced the iM signal and *Lhb* mRNA, eRNA and lncRNA expression levels dramatically. We thus present novel elements in the regulation of *Lhb* transcription through various classes of non-coding RNAs and DNA structures, while emphasizing the complexity of transcriptional regulation via context-dependent cis-acting elements.

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The increase in DHEA and its role in reproduction maturation: insights from the spiny mouse model

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Adrenarche is the postnatal development of the Zona reticularis (ZR) layer of the adrenal cortex starting as early as 3 years of age and can be detected clinically in children at about 6-8 years old. Adrenarche leads to the production of the steroid hormone dehydroepiandrosterone (DHEA), a precursor of testosterone and estradiol, possibly mediating their effects 2-3 years prior to puberty onset. In recent years, there is growing evidence showing a connection between premature adrenarche, earlier pubertal events and the development of polycystic ovarian syndrome, suggesting a role for prepubertal DHEA increase in pubertal development. One of the challenges in the research of adrenarche is the lack of a suitable animal model since adrenal

synthesis of DHEA is only known to occur in humans and some non-human primates. Recently, it was shown in a little rodent, the Egyptian spiny mouse (Acomys cahirinus). We compared gene expression of reproductive tissues between pre-adrenarcheal and adrenarcheal spiny mice using RNA-seq. The adrenarcheal mice had higher DHEA serum levels, although both groups are pre-pubertal. We found a ZR-like morphology in adrenals of adrenarcheal spiny mice, suggesting it to be the origin for the increased DHEA. The mRNA levels of gonadotropin receptors and steroidogenic enzymes were higher in the adrenarcheal spiny mice, even though there was no change in the mRNA levels of the gonadotropins in the pituitary. We identified estrogen receptor as a common regulator of adrenarche-associated differentially expressed genes in the ovary, by searching for enriched motifs in their promoters. We further found estrogen receptor to mediate the induction of pituitary prolactin by DHEA. Since prolactin is suggested as an activator of adrenal DHEA production, we speculated there is a positive feedback loop between pituitary prolactin and adrenal DHEA production. Nonetheless, there was no change in mRNA levels of steroidogenic enzymes in cells treated with prolactin and no correlation between adrenal mRNA levels of prolactin receptor and DHEA serum levels in spiny mice. Interestingly, DHEA serum levels of spiny mice negatively correlated with mRNA levels of dopamine receptor in their adrenals. This evidence and previous research showing the effect of dopamine agonists on DHEA adrenal production led us to suspect that lower dopamine inhibition at adrenarche might contribute to the increase in DHEA at this developmental stage. This elevation in DHEA can affect pre-pubertal prolactin transcription and ovarian gene expression, through activation of estrogen receptor, which might promote ovarian maturation and pubertal timing.

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Over-Representation of Adoptees among Transgender Subjects Seeking Gender-Affirming-Hormonal-Therapy (GAHT) in a Large Tertiary Medical Center.

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Background: The etiology of transgenderism is still unclear. Possible mechanisms range from inborn brain-specific anatomical characteristics, to endocrine-related genetic polymorphisms. In addition, psychosocial developmental factors, particularly trauma from early childhood, are believed to contribute. In line with a handful of previous reports, we were struck by what seemed to be an over-representation of adoptees among adult subjects seeking GAHT at our Transgender Health Center.

Aims of Study: To confirm that adopted individuals are more likely to seek a gender transition process than nonadopted subjects, and to determine whether there are major differences between the 2 subgroups.

Design and Methods: A retrospective study of treatment-naïve adult subjects seeking GAHT at our center between 01.05.2014 and 31.12.2022. The prevalence of adopted subjects in the cohort was compared with the national rate by one sample binomial test. Adoptees were compared to nonadopted subjects in the cohort by nonparametric tests.

Results: During the study period, 671 new adult transgender subjects initiated GAHT at our clinic. Among them, 14 adoptees or 2.09%, which is an order of magnitude greater than the corresponding national rate of 0.22% (P0.0001). This rate is lower than that reported from clinics for transgender youth in Canada (7.6%), in the US (8.2%), and in Britain (3.8%). Age of adoption was at, or below, one year in 13 cases, and at age 2.7 yr in one.

The distribution of assigned-at-birth sexes was different between the 2 groups. Among the 657 nonadopted subjects, the breakdown was quite balanced, 323 had been assigned male sex (49.2%), and 334 female (50.8%). Among adoptees, only 3/14 (21.4%) were born males, and 11 (78.6%) females, P=0.056, by Fisher’s exact test. There was also a trend for adopted subjects to be somewhat older than non-adopted subjects. Their median age was 25.5 yr [IQR 23-30.75], as opposed to 23 yr [IQR 19-30] in non-adopted

subjects, P=0.08. Characterization, and comparisons of parameters such as socioeconomic status, co-morbidities, and others, are still ongoing.

Conclusions: There is an over-representation of adopted adults requesting GAHT at our center. However, the rate is lower than what has been reported from pediatric clinics, suggesting some of these subjects may seek help at a younger age. The findings support a contributory role of adoption in early infancy and the trauma around it in the development of transgenderism. Further research should attempt to decipher the mechanisms through which this early life event interacts with inborn properties.

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Differences in Sex Development – The Clinical Experience of a Tertiary Care Center

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Introduction: Differences in sex development (DSD) comprise a heterogeneous group of congenital conditions that affect human sex determination and differentiation. We aimed to describe the clinical diagnoses of children with DSD who were referred to a pediatric tertiary center, and to examine trends in clinical features and management over three decades.

Methods: This is a retrospective, cross-sectional study of children with DSD who were under our care during 1990-2019. The cohort was sub-classified by DSD class and by the year of diagnosis: before and after the introduction of the current DSD consensus guidelines in 2006.

Results: The cohort included patients with 46, XY DSD (n=87, 78.5%); 46, XX DSD (n=15, 13.5%); and chromosomal DSD (n=9, 8%). For patients with 46, XY DSD compared to patients with 46, XX DSD, the mean age at presentation was younger (0.5±2.5 vs. 6.8±8.1 years, p=0.007), and a higher proportion presented by age 1 year (94% vs. 60%, p=0.001).

Forty-four children were diagnosed during 1990-2006, and 67 during 2007-2019. While the proportions of DSD classes were similar between the two periods, prenatal diagnosis was more common in the recent years: 25.4% vs. 4.5% of the patients, p=0.004. Gonadectomy was performed in 22.9% of 46, XY patients; 6.6% of 46, XX patients; and 67% of chromosomal DSD patients. During 2007-2019 compared to 1990-2006, the proportions were lower of patients who underwent gonadectomy (16% vs. 36%, p=0.02), and of patients who had sex reassignment (1.5% vs. 11%, p0.04).

Conclusions: An increase in the rate of prenatal diagnosis, and declines in the rates of gonadectomy and sex reassignment were shown over the course of three decades. Earlier diagnosis and the introduction of new advanced diagnostic tools enabled earlier and better management, using a patient-centered approach, by a multidisciplinary team.

CNS Manifestations are Linked with Hot Flashes: Analysis of Real-World Data from a Social Network

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Background: Hot flashes, a hallmark of the menopausal transition, frequently coincides with CNS manifestations of disturbed sleep, cognition, and mood. How these relate is an active area of research.

Objective: To evaluate the association of hot flashes with specific CNS manifestations in real world settings of social media.

Methods: We downloaded 4772 posts from Reddit's Menopause group. 586 randomly sampled posts were labelled for their relevancy to menopause. Relevant posts were further labelled for mentions of hot flashes, cognition, reports of adverse mood, sleep problems and reported age. A random forest model for identifying relevant posts from words and bigrams of the posts was trained using the labelled samples and its performance evaluated using 10-fold cross-validation. The model reached an Area Under Curve (AUC) of 0.77. The model was used to filter the remaining posts by selecting posts classified as having a 75% or more likelihood of being about menopause\perimenopause. This resulted in 3546 posts from 1854 users. Models for the remaining labels were trained, reaching AUCs of 0.70 to 0.79. The models were applied to the unlabeled posts. Labels with a prediction in the range of 33-66% were removed to keep only those for which models provided strong indications. Posts were aggregated by user and the average score for each predicted label was computed.

Main Outcome Measures: The ratio of women reporting one of three outcomes; disturbances in cognition, mood, or sleep, from all women with or without hot flashes.

Results: The average stated age was 44.3 years (range: 21-59, N=165). In the whole cohort, hot flashes were reported in 32%, adverse mood in 40%, impaired sleep in18% and cognitive disruption in 15% of women. In women with hot flashes, adverse mood occurred in 46.9%, impaired sleep in 27.2%, and cognitive disruption in 25.3%. In women without hot flashes adverse mood occurred in 4.3%, impaired sleep in 0.7% and cognitive disruption in 0.7%. Results are statistically significant (chi2 test) at P10^(-10).

Conclusions: Hot flashes, which occurred in a third of the women, were individually associated with disturbances in mood, sleep and cognition. Adverse mood was highly prevalent and should be actively sought and addressed.

Glucocorticoid Resistance Syndrome: A Challenging Diagnosis

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A 68-year man presented to our clinic seeking a second opinion regarding pituitary surgery for a suspected corticotroph adenoma. He was diagnosed with hypertension at 25 and osteoporosis at 65. He has practiced intense physical exercise for ten years but quit due to myalgia. During the following seven years, he gained 28 kg; therefore, he considered bariatric surgery. In the physical examination, there were no signs suggestive of hypercortisolism. The routine screening revealed urinary-free cortisol (UFC) excretion of 1415 nmol/24h (N- up to 208), serum cortisol 264 nmol/L after administration of 1 mg dexamethasone, and midnight salivary cortisol within the normal range. Baseline serum cortisol and ACTH ranged from 618 to 713 nmol/L and 5-7.8 pmol/L, respectively. The 8 mg overnight dexamethasone suppression test was normal (cortisol 48 nmol/L), and a CRH test suggested non-neoplastic cortisol secretion. The working diagnosis was non-neoplastic hypercortisolism; therefore, he received clearance for a sleeve gastrectomy in 2014, followed by a 33 kg weight loss. In 2017, he underwent excision of an enlarging left adrenal mass found to be adenomatoid cortical hyperplasia. After surgery, serum ACTH increased to 30 pmol/L with persistently elevated serum and urinary cortisol levels.

The workup for ACTH-dependent Cushing syndrome included a normal pituitary MRI and a normal octreotide scan. The patient received treatment with ketoconazole up to 1200 mg daily, during which there was a pronounced increase in blood pressure that was previously well controlled, accompanied by leg edema. UFC dropped to 289 nmol/24h, but treatment was discontinued due to side effects.

A repeat MRI identified a small arguable pituitary finding; therefore, he was referred to pituitary surgery, whereon we were consulted.

The development of hypertension and leg edema suggested that a ketoconazole-driven decrease in cortisol led to a further increase in ACTH levels with the shunting of cortisol precursor products to the mineralocorticoid pathway in the presence of a mutation in the glucocorticoid receptor. The diagnosis of glucocorticoid resistance syndrome was further supported by the absence of cushingoid appearance, young age hypertension, adrenal hyperplasia, and preserved diurnal cortisol secretion. NR3C1 gene sequencing revealed a novel likely pathogenic heterozygous variant c.1330TG p.Phe444Val; located in a functional domain and is predicted to affect protein function.

In conclusion, diagnosing glucocorticoid resistance syndrome is challenging but should not be overlooked in patients with ACTH-dependent hypercortisolism, as misdiagnosis may lead to unnecessary and potentially harmful treatment.

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Body composition in pediatric celiac disease and metabolic syndrome component risk-an observational study

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Background: Celiac disease (CD) in children and adolescents has been linked with increased susceptibility for cardiometabolic disease in adulthood. We explored the interaction between body composition and metabolic syndrome (MetS) components in pediatric CD.

Methods: We conducted a retrospective observational study of patients with CD followed at our Pediatric Endocrine and Gastroenterology Units between 1/2018-1/2022. Data on sociodemographic, clinical, laboratory, and body composition parameters (bioelectrical impedance analysis, BIA) were collected.

Results: Forty-four patients with MetS components and 67 patients without them were enrolled. The cohort`s mean age at BIA assessment was 11.5 ± 3.6 years. Individuals with MetS components were older (P = 0.045), had higher BMI z-scores (P 0.001), higher total and truncal fat percentage levels (P 0.001), lower muscle-to-fat ratio z-scores (P = 0.018), higher sarcopenic indices (P = 0.05), higher systolic blood pressure percentiles (P = 0.001), higher triglycerides levels (P = 0.009), and higher triglycerides/HDL-c ratios (P 0.001) than those without MetS components. A sex- and age-adjusted model revealed that the diagnosis of MetS components was positively associated with fat percentage (odds ratio = 1.087, confidence interval [1.010-1.171], P = 0.027), but not with BMI z-scores (P = 0.138).

Conclusions: We found that fat percentage but not weight status is associated with risk for MetS components in individuals with childhood-onset CD. Preventive interventions should target an improvement in body composition.

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Deciphering Liver Glycome Regulation by the PGC-1/FN3K Axis

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Introduction: Diabetes in general, and specifically in the context of obesity, is characterized by hyperglycemia resulting in non-enzymatic glycation of proteins. Yet, the full scope of molecular targets for glycation, particularly in liver, is incompletely understood. De-glycation, which removes the attached sugars, is controlled intracellularly by fructosamine-3-kinase (FN3K). However, whether intracellular de-glycation is regulated in physiological contexts and what factors are involved in its regulation remain unknown.

Aim: To identify factors controlling the regulation of FN3K and protein glycation in liver.

Methods: Gene expression analysis in mouse liver and cell culture experiments with overexpression of the key metabolic regulators PGC-1s (PGC-1a and PGC-1b). Mass spectrometric analysis was used to monitor protein glycation.

Results: Our data identify that regulation of protein glycation in liver is controlled by the key metabolic regulators PGC-1s in response to metabolic cues, particularly in the fed state. Liver-specific deletion of PGC-1s results in global changes in gene expression as determined by RNA-seq, among which is reduction of Fn3k expression and concomitant increase in specific protein glycation. In accordance, overexpression of PGC-1a in primary hepatocytes and in liver-derived cell lines induces Fn3k mRNA and protein levels and

reduces protein glycation. In human liver cancer samples, expression of Fn3k mRNA is significantly correlated with PGC-1a mRNA expression. Purification of glycated proteins followed by mass spectrometric analysis and subsequent validations reveal significant alterations in intracellular protein glycation in response to PGC1-a expression. Mechanistically, PGC-1a effect on Fn3k is transcriptional, and a fragment from the Fn3k gene is identified as a regulatory element mediating the effect. Additionally, PGC-1a regulation of Fn3k involves the activity of the transcription factor Foxo1, as Foxo1 inhibition dampens PGC-1 induction of Fn3k expression.

Conclusions: In liver, fasting and re-feeding govern intracellular protein glycation via PGC-1 dependent induction of FN3K. Our work reveals the scope and dynamic nature of the liver glycome, establishing the PGC1/FN3K axis as a key regulator of protein glycation.

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Cardiovascular Outcomes of Glucose-lowering Pharmacological Agents in Older Adults- Systematic Review and Meta-analysis

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Background: The prevalence of diabetes mellitus increases with age, estimated as 15-30% in those over 65. Recent studies have examined the cardiovascular safety of glucose lowering agents. However, a small number of older people were included, therefore data on older adults is lacking.
Objective: To examine the cardiovascular safety of glucose lowering agents in older diabetics.
Methods: Electronic databases search: Medline, The Cochrane Library, EMBASE, Trial Registration Database. Additional studies were searched by utilizing the reference lists of included trials, systematic reviews and meta-analysis. The final list was reviewed by an expert in the field to verify its completeness.

This systematic review and meta-analysis included randomized controlled trials (RCT) that evaluated the effect of a single glucose lowering pharmacological agent versus other drug (standard of care) on cardiovascular outcomes in adults with type 2 diabetes, males and females. Trials comparing strategies other than glucose lowering pharmacological agents were excluded.

Validity was assessed utilizing "the Cochrane collaboration`s tool for assessing risk of bias". Data was extracted using an adapted data extraction form.
This meta-analysis used the fixed effects model and random effects model. Results were presented using a forest plot. Publication bias was assessed using a funnel plot.

Results: 30 studies fulfilled all inclusion and exclusion criteria and were included in this review. 17 studies could be analyzed. Most trials had a low risk of bias. The main analysis included 62132 older adults (65) and 9008 elderly adults (75) with type 2 diabetes and demonstrated that glucose lowering pharmacological agents have a neutral or positive effect (GLP-1-RA trials) on cardiovascular safety and efficacy in older adults, similar to the effect observed for the overall diabetic population in all pharmacological groups.

Studies included in this SR excluded patients with high comorbidity. ~10% of all study participants were elderly adults.

Conclusions: This systematic review and meta-analysis highlights the low representation of older adults in RCT of glucose lowering agents. It demonstrates that in older people able to participate in RCT the efficacy is similar to younger individuals and with some of the drugs the effect is even more pronounced. In light of the increase of diabetes with age and the rise in life expectancy there is a need for further clinical trials representing higher proportions of older people with varying characteristics, including cognitive status, functional status and severe comorbidities.

Glucagon-like peptide 1 receptor agonists and cardiovascular outcomes in solid organ transplant recipients with diabetes mellitus

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Background

Post-transplant diabetes mellitus is diagnosed in 30% of solid organ transplant recipients. Limited data is available on use of anti-hyperglycemic drugs in this population. Beyond their anti-diabetic effect, glucagon-like peptide-1 receptor agonists (GLP1-RAs) are considered disease-modifying drugs, in particular due to reduction in cardiovascular events and mortality in patients with type 2 diabetes. We aimed to explore the effect of GLP1-RAs on cardiovascular outcomes in transplanted recipients.

Methods

Retrospective analysis. We included adult transplant recipients (kidney, lungs, liver, heart) insured in Clalit Health Services (Dan-Petah-Tikva and Tel-Aviv districts). Death-censored diabetic patients treated with GLP1RAs were matched with non-users. Only GLP1-RAs with proven cardiovascular benefit (liraglutide, dulaglutide, semaglutide) were included. The primary outcome was a composite of major cardiovascular events (MACE): a non-fatal cardiac vascular event (myocardial infarction, stable/unstable angina, coronary bypass, coronary angiography), ischemic stroke and all-cause mortality. Secondary outcomes were a new diagnosis of MACE or peripheral vascular disease (MACE-PVD), and all-cause mortality. These outcomes were adjusted for gender, age, socioeconomic status and history of MACE-PVD. Safety outcomes included biliopancreatic adverse events.

Results

Five hundred and fourteen patients were included (257 in each arm). The estimated median time to the primary composite outcome (MACE) was 5.4 years in patients treated with GLP1-RAs versus 4.4 years in non-users (HR 0.780, 95% CI 0.585-1.040). Occurrence of MACE-PVD showed similar trend for a lower risk in users of GLP1-RAs (HR 0.784, 95% CI 0.593-1.038). Risk of all-cause mortality was lower in users of GLP1-RAs (HR 0.578, 95% CI 0.357-0.936). Biliopancreatic adverse events occurred less in patients treated with GLP1RAs.

Conclusions

As post-transplant diabetes mellitus is an exclusion criterion in large randomized controlled trials of diabetes therapy, the efficacy of anti-hyperglycemic drugs in solid organ transplant recipients remains under-investigated. Use of GLP1-RAs in solid organ transplant patients shows a trend for a protective effect from cardiovascular adverse outcomes. Risk of all-cause mortality was significantly lower in GLP1-RA users. Larger prospective studies are needed in this unique population.

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Xenograft of *VHL*-deficient pancreatic neuroendocrine neoplasm cells - a novel low-grade PNEN *in vivo* model

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Background: Von Hippel-Lindau (VHL) disease is a familial cancer syndrome caused by a germline mutation in the VHL tumor suppressor gene. Although VHL-related pancreatic neuroendocrine neoplasms (vPNEN) have been studied, their molecular pathogenesis is not fully understood. Aims: To generate a mouse model for studying the mechanism promoting vPNEN development in vivo. Methods: We introduced a frameshift mutation in VHL using CRISPR/Cas9 technique in BON1 cell line, originating from high-grade PNEN (FS-BON1). The pseudohypoxic nature of the cells was validated by real time polymerase chain reaction of VEGF and EPO in FS-BON1 compared to VHL wild type BON1 (WT-BON1). We compared cell line derived xenografts (CDXs) growth in athymic Nude-Foxn1nu female mice, injected with WT-BON1 (n=9), FS-BON1 (n=9) and purified bovine serum (n=5). Tumor diameter and calculated volume, and mice weight were recorded weekly. Plasma chromogranin A (CgA) levels were measured in mice sera by ELISA. Subcutaneous, local tumors were harvested, immediately divided. The derived "tumors" were processed for histopathology for quantifying expression of synaptophysin, CgA and KI-67. Additionally, the xenografts were processed for polar metabolites screen and analyzed using the MetaboAnalyst web-based metabolomics analysis tools. Results: FS-BON1 cells showed upregulation of VEGF and EPO compared with WT-BON1, confirming their pseudohypoxic nature. At 14 weeks, none (0/9) of the FS-BON1 CDX reached volume of 1 cm3 compared with 5/9 of the WT-BON1 group (p=0.03). FS-BON1 derived-xenografts grew significantly slower than WT-BON1 xenograft (Log-rank test, p=0.02). The slow growing FS-BON1 CDXs stained significantly less for Ki-67, a proliferative index, compared with WT-BON1 CDX-tumor in comparison to this in FS-BON1 CDX-tumors. The metabolomics analysis demonstrated a higher representation of glycolysis-related metabolites in the FS-BON1 CDX and higher Krebs Cycle-related metabolites in the WT-BON1 cells. Conclusions: We report a novel in vivo pseudohypoxia-related PNEN model. The pVHL-deficient cells show unexpected indolent course, suggesting it as a new model for low-grade PNEN. This CDX mouse model can be utilized for evaluating the mechanism responsible for vPNEN development and potential interventions in low-grade PNEN.

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Trajectories of Pituitary Height and Endocrine Function in survivors of childhood and adolescence brain tumors.

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Background: Multiple studies demonstrated hypothalamic–pituitary dysfunction in survivors of pediatric brain tumors, however few studies investigated the trajectories of pituitary height in these patients and their association with pituitary function.

Aim: To evaluate longitudinal changes of pituitary height in children and adolescents with brain tumors, and their association with endocrine deficiencies.

Methods: 193 patients (males=54.9%) with a diagnosis of brain tumor before age 18 years, who had at least two years of radiological follow-up after diagnosis were included in this retrospective study. Patients who had tumors involving the sellar/suprasellar region or the hypothalamus were excluded, as pituitary morphology and function could have been affected by the tumor itself or by surgery. Pituitary height was measured on MRI scans performed at the time of diagnosis, and 2, 5, and 10 years thereafter. Demographic, clinical and anthropometric data were obtained from the patients' charts.

Results: The mean age at the time of diagnosis was 7.6±4.5 years, and the mean time of follow-up was 6.1±3.4 years. The most frequent tumor type was low-grade glioma (45.1%), followed by medulloblastoma (21.8%) and high grade glioma (10.3%). One-hundred and two patients (52.8%) were treated with radiotherapy; of these, 53 patients were treated with CSI. Seventy-three patients (37.8%) had dysfunction of at least one pituitary hormone. Regression analysis identified radiation treatment as a predictor of pituitary height at all three post-treatment time points (p=0.016, p0.001, p=0.008, respectively). In addition, pubertal status was identified as a predictor of pituitary height at the 2-year time point (p0.001), age at MRI was identified as a predictor of pituitary height at the 5-year time point (p=0005), and having at least one endocrine deficiency was a predictor of pituitary height at the final follow-up point. History of chemotherapy (p=0.004) or radiotherapy (p=0.022) and pituitary height at the 10-year time point (p=0.047) were identified as predictors of endocrine deficiencies. Pituitary measurements for all four time points were available for 60 participants. ANOVA for repeated measures showed a significant increase in pituitary height over time (p0.001), as expected in pediatric patients. There was a significant difference in change in pituitary height between participants with or without a history of radiation treatment (p for interaction = 0.005) as well as between males and females (p for interaction=0.025).

Conclusion: cranial irradiation in pediatric patients is associated with impairment of the physiologic increase in pituitary size; in turn, decreased pituitary height is associated with endocrine dysfunction.

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Controlling gene expression in gastric endocrine cells using Adeno-Associated virus

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The gastrointestinal (GI) system plays a vital role in nutrient absorption and energy homeostasis, which are tightly regulated by various hormones secreted by the endocrine cells in the gastric corpus and antrum. These cells secrete different types of hormones that control various physiological mechanisms in the body, such as appetite regulation, acid secretion, and gut motility. However, despite the importance of these cells, there is no effective way to manipulate their expression, making it challenging to study their functions and potential therapeutic applications.

To address this challenge, we developed a gene therapy approach to infect the gastric epithelium, including gastric endocrine cells with Adeno-associated virus serotype 9 (AAV9) and AAV2.
Prior to administering the virus, we treated mice with anti-acidic drugs and agents that reduced mucus in the gastric epithelium for seven days. On the day of virus administration, we first gave the mice ketamine to reduce gastric motility, followed by sodium bicarbonate to lower stomach acidity. Then, we administered the virus through gavage.
We used an AAV9 that expresses Cre and green fluorescent protein (GFP) on mice with Rosa-LSL-tdTomato to indicate infection and that the virus is working.

Our results indicate that we can effectively infect chromogranin A-positive (ChgA+) cells in the epithelium, with no mesenchymal infection. We estimated a minimum of one cell per crypt, demonstrating that our method can induce gene expression in the gastric epithelium, specifically in endocrine cells. Furthermore, we can leverage this method for various applications, including disease modeling, such as gastric cancer, over-expression of gastric and non-gastric hormones, gene silencing, gene therapy, and synthetic biology.

In conclusion, our gene therapy approach provides a promising avenue to manipulate gene expression in the gastric epithelium, specifically in endocrine cells. This methodology offers vast potential for developing new therapeutic interventions for GI-related disorders and may lead to a better understanding of the fundamental mechanisms underlying these diseases.

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Can radiation absorbed doses after ^{177}Lu-PRRT be estimated from a single SPECT/CT study: Validation of a MLR model and impact on patient management for 192 therapies.

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INTRODUCTION:

Dosimetry calculation after 177Lu-DOTA-TATE Peptide Receptor Radionuclide Therapy (PRRT) enables to estimate radiation doses absorbed by normal organs and target lesions. However, the process is time-consuming and requires multiple post-treatment studies on several subsequent days. In a previous study [1], we described a newly developed multiple linear regression (MLR) model to predict absorbed doses (ADs) from a single post-treatment study. The model takes as input the time of imaging and the volume and counts in a given tumor/organ VOI. The aim of the present study was to validate this single time-point dosimetry model in a large number of patients and to assess whether single time-point dosimetry maintains management decisions related to the continuation of PRRT as compared to multiple dosimetric measurements.

MATERIAL AND METHODS:

Quantitative 177Lu-DOTA-TATE SPECT/CT data obtained after PRRT of 178 consecutive patients with metastatic neuroendocrine tumors for a total of 192 treatments and 541 therapy cycles were retrospectively analyzed for validation of the model. The predicted single time-point ADs were compared to those obtained using the standard multiple time-point protocol. Subsequently, the impact of the single time-point dosimetry protocol on patient management decisions, i.e. the decision whether PRRT can be safely continued or should be stopped because of “expected” AD exceeding the safety threshold to kidneys, was evaluated. The null hypothesis was that patient management decisions using the single time-point protocol will differ from those made using the standard protocol in more than 5% of therapies.

RESULTS:

The difference in management decisions between the standard protocol and the single time-point model was 1.0% (p 0.003). Cumulative ADs were obtained with mean relative differences of 0.6% ± 8.2%, 3.4% + 13.7%, -0.5% ± 10.8%, 2.2% ± 6.5% and -3.6% ± 17.7% for kidneys, bone marrow, liver, spleen and tumors, respectively (Pearson’s r correlation coefficients 0.96 for bone marrow and 0.99 for all others).

CONCLUSIONS:

Present study confirms the high accuracy of the single time-point model for estimation of the radiation ADs by organs and lesions. This model can be therefore used with confidence, simplifying the dosimetry process without the need to use of laborious time-consuming software, while also reducing scanner and staff time and most important improve patient comfort.

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Single-Nucleus RNA sequencing-based characterization of sporadic and VHL related Pancreatic Neuroendocrine Neoplasms (PNEN)

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Background: Von Hippel Lindau (VHL) is a hereditary syndrome characterized by the presence of multiple neoplasms and is caused by a genetic alteration in the VHL tumor suppressor gene. Patients with VHL are susceptible to the development of PNENs, among other neoplasms.

Objective: In order to gain a deeper understanding of the pro-tumoral factors and potential targeted interventions, we conducted single nucleus RNA sequencing (snRNA-seq). This allows analysis of gene expression at the single cell level and can provide valuable insights into the molecular differences between sporadic (sPNEN) and VHL-associated PNENs (vPNEN).

Methods: Our study involved snRNA-seq analysis of ten samples, with five samples each from the sporadic and VHL-associated groups. Ten tissue samples (5/5 vPNEN/sPNEN) were processed and sequenced for snRNA-seq analysis via 10X platform. Analysis was done on R-Studio: clustering and annotation were executed using the Seurat package, and copy number alternations were detected utilizing the InferCNV package, and allowed identification of the malignant neuroendocrine cells.

Results: Our study involved snRNA-seq analysis of ten samples, with five samples each from the sporadic and VHL-associated groups. Through a comparison of the transcriptomes of cells from these two groups, we identified distinct subclusters of various cell types. The most significant difference observed between the two groups was the presence of immune cells in vPNETs, whereas they were present in sPNETs in a reduced amount.

In addition, following the identification of neuroendocrine malignant cells, we discovered similar patterns of chromosomal alterations, including frequent losses at chromosomes 1, 2, 3, 6, 11 and gains at chromosomes 4, 5, 7, 12, 19, and 20, in both sPNETs and vPNENs.

Conclusion: The identification of immune cells within the samples of vPNETs presents an intriguing finding that warrants further investigation. This is the first study enabling single-cell based identification of vPNEN, and comparing sPNEN and vPNEN CNAs, representing an avenue for potential future research.

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Mid-treatment Response to 177Lu-DOTATATE Predicts Overall Treatment Outcome in Patients With Neuroendocrine Neoplasms

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Introduction - Patients with advanced or unresectable neuroendocrine neoplasm (NENs) have limited systemic treatment modalities. Among these, patients with well-differentiated, G1 and G2, somatostatin receptor-expressing NENs can be treated with peptide receptor radionuclide therapy (PRRT) treatment with 177Lu-DOTATATE. Since a subset will require further chemotherapy in later stages, limiting radiation exposure is of paramount importance. Nevertheless, there are no mid-treatment predictive factors for response to PRRT.

Aims – To assess the utility of mid-treatment (post 2nd cycle) response to PRRT as a marker for overall treatment efficacy in patients with well-differentiated NENs.

Materials and Methods - A retrospective study in a tertiary center, enrolling patients that underwent at least four cycles of PRRT. Data gathered included demographics, tumor grade and stage, treatment response (partial response [PR], stable disease [SD] or progressive disease [PD]) evaluated by 68Ga-DOTATATE PET CT at baseline and after 2nd and 4th treatment cycle, six months after 4th treatment cycle and at last follow-up.

Results - A total of 31 patients (51.6% women, age at diagnosis 62.8±1.8 years) completed four PRRT cycles (median, range 4-6). NEN primary sites were pancreatic (n=15), small intestine (n=9), lung (n=2), or other (n=5). The outcomes after four PRRT cycles were PR, SD, and PD in 14, 13, and 1 patients, respectively. Patients with pancreatic NEN (PNET) had superior response vs. small intestine NEN (SiNET, p=0.005). Patients with PR at mid-treatment had higher PR rates at final evaluation than those with mid-term SD (p=0.004), but not at 6 months or at the last follow-up (p0.05 for both comparisons). On multivariable model, adjusted for age, grade, and tumor type (PNET, SiNET, or other), mid-treatment outcome was independently associated with final outcome after 4 PRRT treatments (adjusted odds ratio 9.9, 95% confidence interval 1.2-82.1, p=0.03).

Conclusions – Mid-treatment PRRT efficacy can serve as a measure for overall PRRT efficacy in patients with advanced or unresectable well-differentiated NEN.

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Reversible Pro-oncogenic Effect of Netrin - DCC Interaction on Neuroendocrine Neoplasm Cells

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Background: Netrin is a guidance-cue protein, known for its involvement in neuronal axon growth guidance. One of netrin`s main receptors, deleted in colorectal carcinoma (encoded by DCC), is a dependent receptor that induces distinct downstream activities with vs. without netrin binding: Netrin-free DCC induces apoptosis of neuronal projections while in the presence of netrin DCC exerts their survival. DCC is known for its role as a tumor suppressor, but to a lesser extent as a prooncogenic factor. Repeated somatic alterations of DCC in neuroendocrine neoplasms (NENs) were reported. However, its neoplastic role in neuroendocrine neoplasms is yet to be determined.

Aim: To determine the role of netrin-DCC interaction in NEN tumorigenesis.

Methods: We examined the baseline DCC and Netrin-3 protein expression in the pancreatic NEN cell line BON1 using Western Blot and ELISA, respectively. Then, we compared the impact of DCC and Netrin expression on cells viability using MTT. DCC gene down-regulation was induced via transfection with DCC siRNA, validated by fluorescently-tagged siRNA and real time-PCR. Inhibition of Netrin protein was induced using selective antibody (NP137). Netrin overexpressing environment was achieved using recombinant Netrin-1. SH-SY5Y neuroblastoma-derived cell line served as positive control for netrin secretion and for DCC expression, and the triple negative breast cancer cell line MDA-231 served as a negative control for DCC expression.

Results: Untreated BON-1 cells demonstrated both high DCC gene and protein expression and Netrin-3 excretion compared with SH-SY5Y cells. Furthermore, increased netrin concentrations correlated with increased BON-1 viability ($r=0.91$, $p=0.0015$), while increased netrin inhibitory antibodies concentration had negative correlation with BON1 cells viability ($r=-0.90$, $p=0.001$), while not affecting viability of the DCC-deficient cell line MDA-231 ($p=0.3$). The increased viability with netrin-1 treatment was more pronounced in cells transfected with non-targeted vs. DCC siRNA ($p=0.005$), showing the dependency of netrin-1 effect on DCC expression.

Conclusion: Our data demonstrates a reversible pro-neoplastic impact of netrins in NEN cells, with netrin-DCC interaction dependency. Therefore, the netrin-DCC interaction should be further investigated as a therapeutic target.

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The Effect of a Pseudohypoxic Environment on the Immune System of Pancreatic Neuroendocrine Tumors (PanNET)

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Introduction– Pancreatic neuroendocrine tumors may develop sporadically or as part of an inherited disease, such as von Hippel-Lindau (VHL). VHL disease is caused by a germline pathogenic variant in the VHL gene encoding VHL protein (pVHL). Hypoxia inducible factor (HIF) is responsible for cellular oxygen supply. Its degradation is mediated in normoxic states via ubiquitination and inhibited by pVHL. Hence, pVHL deficiency leads to pseudohypoxia due to HIF overexpression. Several studies suggested immunomodulatory role for HIF in kidney cancer.

Aims– To assess the impact of pseudohypoxia on PanNET immune tumor microenvironment (iTME).

Methods– Whole genome DNA methylation data of 16 vPanNET and 23 sPanNET, processed by Illumine Infinium EPIC Array and analyzed using ChAMP on RStudio. Immune cells compositions were compared using methylation-based deconvolution algorithms (MethylResolver, Robust Partial Correlations, Constrained Projection and Cibersort) and gene set enrichment analysis identified pathways affected in each group based on promoter methylation analysis.

Results– Unsupervised hierarchical clustering of immune-related gene promoter methylation demonstrated separation of vPanNET vs. sPanNET. In GSEA analysis methylation was differentially enriched for immune memory-related genes in vPanNET, and T cells receptors-related genes in sPanNET. Deconvolution algorithms revealed a lower fraction of CD4 and NK cells (p0.05), and immunostaining showed weaker PD-L1 expression in vPanNETs (p =0.037).

Conclusion– Pseudohypoxic vPanNETs have distinct iTME than sPanNET, expressed in immune cells composition and PD-L1 expression.

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Langerhans Cell Histiocytosis With Hypothalamo-Pituitary Involvement: The HEROS Study

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Objective: Langerhans Cell Histiocytosis (LCH) is a rare disease, involving multiple organs including the endocrine system. This multicenter study aimed to characterize patients with hypothalamo- pituitary involvement.

Methods: The Hypopituitarism ENEA Rare Etiologies Observational Study (HEROS) platform invited ENEA members to include patients with rare pituitary diseases including LCH. Demographic data, presenting symptoms, hormonal profile, imaging tests, treatment, and prognosis were retrieved.

Results: 44 patients (27 males) were included, age at diagnosis was 22.7±16.2 years, 26 diagnosed as adults (18) with mean follow up 14.8±26 years. Twenty-one patients presented with bone lesions, 19 with lung involvement, 4 were incidentally diagnosed. At diagnosis, 39 patients presented with diabetes insipidus, 20 patients (15 males) had hypogonadism, 11 with central hypothyroidism and hypocortisolism in 6. Imaging studies were available for 41 patients, 26 had pathology of the posterior pituitary/ the stalk, anterior pituitary mass was depicted in 4 patients, suprasellar mass in 8 patients and empty sella in 9 subjects. Visual disturbances reported in one. Transcranial biopsy was performed in 5 patients, transsphenoidal in 2 patients; Histopathology confirming LCH was reported in 39 patients, mostly of extra-pituitary lesions. During follow-up 11 patients were given glucocorticoids with hormonal improvement in two; 5 received radiotherapy and 15 patients treated by chemotherapy with hypogonadism resolution in one. Prognosis was good and without mortality.

Conclusions: Patients with LCH and hypothalamo-pituitary involvement are stable during long-term follow-up.

Impulse Control Disorders in Patients with Prolactinomas and Non-Functioning Pituitary Adenomas Treated with Dopamine Agonists

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Objective Impulse control disorder (ICD) is a well-recognized side effect of dopamine agonist (DA) treatment in patients with Parkinson's disease and restless leg syndrome. The available data on the incidence of ICD in patients treated with DA for pituitary tumors are sparse. This study aimed to assess the occurrence of ICD among patients with prolactinomas or NFPA treated with DA compared to patients with prolactinomas or NFPA not treated with DA and to patients with non-pituitary endocrine disorders.

Methods: Patients attending the general endocrine and pituitary clinics at the Institute of Endocrinology in our medical center were invited to fill in an anonymous validated questionnaire on hypersexuality, pathologic gambling, compulsive shopping, and punding. Associated relevant clinical information was also obtained.

Results: In total, 174 patients consented to participate. Those with pituitary disorders other than prolactinomas and NFPA were excluded. The final study cohort consisted of 67 patients with NFPA (31 DA-treated) and 40 with prolactinomas (35 DA-treated). The control group consisted of 67 non-DA-treated subjects with other endocrine disorders. The entire cohort was comprised of 77 men and 97 women (mean age 56±17 years). ICDs were reported by 19/66 (29%) DA-treated patients with prolactinomas or NFPA, 3/41 (7%) non-DA-treated patients with prolactinomas or NFPA and 8/108 (7.5%) non-DA-treated patients with prolactinomas, NFPA or other endocrine disorders (p0.001). There were no significant differences in ICD rates between DA-treated patients with prolactinomas compared to those with DA-treated NFPA, or between non-DA-treated patients with either prolactinomas or NFPA and controls. The ICD rate among DA-treated women was significantly higher than that of non-DA-treated women (34.5% and 7.5%, respectively. p0.001). No comparable differences were observed in DA-treated versus non-DA-treated men or between all participating men and women.

Conclusion: ICD rates are significantly higher among patients treated with DA for prolactinomas or NFPA compared to non-DA-treated patients with prolactinomas, NFPA or other non-pituitary endocrine disorders. Patients being treated with DA for any pituitary lesion should be informed of the greater risk of associated ICD.

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Prediabetes in pregnancy – outcomes compared to type 2 diabetes

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Objective

With the growing epidemic of obesity, number of women entering pregnancy with prediabetes and type 2 diabetes is rising. However, there are limited data on follow-up, treatment, and maternal and fetal outcomes in women with prediabetes prior to or at the start of pregnancy. The aim of this study was to comprehensively characterize women with prediabetes compared to women with type 2 diabetes mellitus in pregnancy.

Study Design

This retrospective cohort study included all women attending a multidisciplinary dedicated Diabetes in pregnancy clinic between 1/1/2014 to 31/12/21 who were ≥18 years old and carried a singleton pregnancy. Women with pregestational prediabetes mellitus (PDM) were compared to women with pregestational overt type 2 diabetes mellitus (T2DM) according to ADA guidelines.

Results

Data were collected from 120 women in the PDM group and 86 women in the T2DM group. Women in the PDM group arrived at medical attention significantly later, 55% after 15 weeks gestation. Most baseline characteristics were comparable including age, body mass index (BMI), obesity rates, smoking at the beginning of pregnancy, and obstetric history. About a fifth of the women in each group were nulliparous. Women with T2DM were significantly more likely to report a first-degree family history of diabetes and to be diagnosed with polycystic ovary syndrome (PCOS).

A minority of women were controlled with diet only in the PDM and T2DM groups (8.3% and 3.5%, respectively, P=0.245). The rest were treated with insulin, metformin, or both. Women with T2DM received twice as much metformin to achieve glycemic control compared to PDM (56% versus 23.3%, P=0.001). Women with T2DM were significantly more likely to receive multiple daily injections (MDI) (24% versus 10%, P=0.01), and to use insulin pumps and continuous glucose monitors (CGMs). Thus, overall treatment burden was higher in women with T2DM compared to PDM. However, glycated hemoglobin remained lower throughout pregnancy in the PDM group. Maternal and fetal outcomes were similar between groups, although significantly higher rates of macrosomia and neonatal jaundice were observed in the T2DM group.

Conclusions

The lack of clear guidelines causes a delay in the first prenatal visit of women with PDM. Comparable outcomes suggest that women with PDM need follow-up and treatment as women with T2DM.

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The Role of Adipocyte Connexin-43 in Mediating Adipose Tissue Inflammation and Dysfunction in Obesity

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Obesity is a leading global health concern and a major risk factor for type-2 diabetes. Thus, identifying mechanisms linking obesity to insulin resistance is of great importance. Infiltration of various immune cells and chronic low-grade inflammation of the adipose tissue (AT) observed in obesity have been shown as important pathophysiological links between obesity and the development of systemic insulin resistance, by various mechanisms. Gap junction (GJ) intercellular-communication, primarily composed of connexin-(Cx)43, has been reported to have immunomodulatory roles in various tissues, and recently macrophage Cx43 has been demonstrated to promote infiltration of macrophages into the obese AT and to affect their inflammatory phenotype. We have therefore aimed to study the role of adipocyte Cx43 in shaping the cellular composition of the obese AT and its adaptive or maladaptive response to the cellular insults of obesity.

In a diet-induced obesity mouse model we observed an increase in Cx43 expression in the intact AT, which could be primarily attributed to increased Cx43 expression in adipocytes. Mechanistically, we demonstrated that adipocytes can interact directly with neighboring cells via Cx43-composed gap junctions. In high fat diet-fed adipocyte-specific Cx43 knock-out mice (AdCx43KO), we observed increased expression of leukocyte infiltration gene pathways, and decrease in systemic insulin sensitivity. Analysis of the AT cellular composition by single-nucleus RNA sequencing has identified several changes in the immune cell populations infiltrating the tissue in the AdCx43KO obese AT. Namely, we observed an increased presence of mast cells in these mice, which has been previously linked to a decrease in whole body insulin sensitivity.

Our results suggest an immunomodulatory role for adipocyte-Cx43 in obesity, possibly through direct Cx43-mediated interaction with immune cells.

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Sex differences in body composition in youth with type 1 diabetes and its predictive value in cardiovascular disease risk assessment

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Background: Women with type 1 diabetes (T1D) are more susceptible than men to cardiovascular disease (CVD). Signs of increased risk may already appear among adolescent girls.

Objectives: We explored the contribution of body composition to the development of CVD risk factors among youth with T1D.

Methods: One hundred and eighty nine subjects with T1D (mean age 15.3 ± 5.1 years, 55% boys) followed between January 2018-January 2022 were included in this observational study. Sociodemographic and clinical data were extracted from medical files. Body composition was measured by bioelectrical impedance analysis, and muscle-to-fat ratio (MFR) z-scores were calculated. Logistic regression model assessed the association between body composition (MFR z-scores) and evidence of CVD risk factors.

Results: Females were characterised by higher median BMI z-scores (0.47 vs. 0.04, p = 0.012), higher fat and truncal fat percentage levels ($p \leq 0.001$) and lower median MFR z-scores (-0.64 vs. -0.25, $p \leq 0.001$), higher median triglyceride (TG) levels (71 vs. 61 mg/dl, p = 0.05), longer disease duration to initiation of insulin pump therapy (p = 0.041), and more time spent in marked hypoglycemia (1 vs. 0.2%, p = 0.007) than males. Males` MFR z-scores were associated with several diabetes-related parameters (age at diagnosis, CGM metrics, HbA1c and insulin dose), while the females`` MFR z-scores were linked to the atherogenic dyslipidemia index (TG:HDL ratio). The odds for CVD risk factors were doubled for every 1 SD decrease in MFR z-score (OR = 0.50, CI [0.30-0.84], p = 0.009) and also increased with age (OR = 1.07, CI [1.004-1.148], p = 0.038).

Conclusions: Body composition measurement has a predictive value in CVD risk assessment in youth with T1D, with unique characteristics and influences in each sex.

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The Metabolic Role of Somatostatin in Sleeve Gastrectomy

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First discovered as the inhibitor of Growth hormone, somatostatin (SST) is a neurotransmitter and a hormone expressed in the hypothalamus, enteric nervous system, stomach, intestine, colon and pancreas. SST signaling inhibits secretion of hormones, neuronal activity and exocrine function of many cell types.

Surprisingly SST knockout (SST-ko) mice display a rather normal phenotype. We challenged the SST-ko mice with a high fat high sucrose diet and found they have lower levels of liver triglycerides compared to their heterozygous littermates. In contrast, the total body fat percent was higher in the SST-ko mice, as measured by MRI. Using a continuous glucose monitor we observed that SST-ko mice have a wider variance of glucose levels and maintain lower glucose levels with higher levels of Glp-1, an intestinal hormone that stimulates insulin secretion and induces satiety.

Bariatric surgery leads to weight loss, and hypersecretion of several gastrointestinal and pancreatic hormones that are normally repressed by SST. We performed sleeve gastrectomy (SG) or sham surgery on SST-ko mice and their heterozygous littermates and observed that SST-ko mice regained less weight, had lower glucose and better glucose tolerance than all other groups. Mechanistically, these mice had high fasting levels and a powerful postprandial surge of Glp-1.

Daily injections of a somatostatin receptor inhibitor following SG produced similar results to those we observed in SST-ko mice following SG: Inhibitor treated mice regained less weight, had lower glucose levels and higher levels of Glp-1 following combined treatment of the surgery and inhibitor.

Somatostatin plays an important metabolic role in sleeve gastrectomy by inhibiting the production of hormones that contribute to weight gain and glucose intolerance. Inhibiting somatostatin signaling can be an effective strategy for improving weight loss and glucose tolerance following sleeve gastrectomy.

Persistent Post-Bariatric-Surgery Hypoglycemia: a Long Term Follow up Reassessment

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Background and aim

Post-bariatric-surgery hypoglycemia (PBH) is a serious complication of bariatric surgery (BS). In our previous study, ``Symptomatic and Asymptomatic Hypoglycemia post three different bariatric procedures: a common and severe complication``, published in Endocrine Practice- 2019, about three quarters of the patients developed PBH, mostly asymptomatic, implying an unawareness phenomenon. However long-term follow-up data is lacking to determine whether this condition improves with time. The aim of the current study was to re-assess post-BS patients who participated in our previous study and determine whether there are changes in the frequency and/or severity of hypoglycemic events.

Methods and Results: we conducted an observational follow-up re- assessment. Twenty-four, out of forty-three patients who participated in our original study, were reevaluated in the current re-assessment: post Roux-en-Y gastric-bypass (RYGB=10), post omega-loop gastric-bypass (OLGB=9) and post sleeve-gastrectomy (SG=5). The median time for reevaluation was 34.4±4 months after their previous assessment and 67±17 months since surgery. The evaluation included: a dietitian assessment, a questionnaire, meal-tolerance test (MTT) and a one-week masked continuous glucose monitoring (CGM). Hypoglycemia and severe hypoglycemia were defined by glucose levels ≤54 mg/dl and ≤40 mg/dl, respectively. In the 19 patients who declined to participate in the current study, after providing a call-phone informed consent, we obtained data on hospitalizations and follow-up clinics visits due to hypoglycemia from electronic data base. The main reason for patients who declined to participate was the need to arrive to the hospital’s outpatient clinic during the COVID-19 pandemic.

Thirteen patients reported questionnaire meal-related complaints, mainly non-specific. During MTT, hypoglycemia occurred in 75% of the patients, and severe hypoglycemia in a third, but none was associated with specific complaints. During CGM, 66% of patients developed hypoglycemia and 37% had severe hypoglycemia. We did not observe significant improvements in hypoglycemic events compared to the previous assessment. Despite the high frequency of hypoglycemia, it did not necessitate hospitalizations or lead to death.

Conclusions: Our study demonstrates that PBH, including unawareness hypoglycemia, remained a very common complication after the three types of bariatric procedures, and persisted after on average more than five years since surgery. In the view of the high frequency of hypoglycemia unawareness we question the recommendation that only PB patients who present with the Whipple triad should be evaluated for PBH. Further large-scale studies are needed to determine the true prevalence and timing of PBH and the impact on morbidity and life-quality of these patients.

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Phytocannabinoids for Treating Obesity-Related Non-Alcoholic Fatty Liver Disease

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Introduction: Obesity, a chronic progressive disease that is now reaching epidemic proportions globally, has been described as a catalyst for cardiovascular disease, type 2 diabetes, and non-alcoholic fatty liver disease. Cannabis, via its non-psychoactive phytocannabinoids, has been shown to reduce weight gain, improve insulin sensitivity, and decrease hepatic triglyceride accumulation in murine models of obesity. However, whether cannabidiol (CBD) and/or cannabigerol (CBG) have the potential to treat obesity and its metabolic abnormalities has never been reported yet.

Methods: The therapeutic potential of CBD (5 mg/kg/day, IP) and/or CBG (12.5 mg/kg/day, IP) on hepatic steatosis, glucose and insulin homeostasis, dyslipidemia, and body weight gain was evaluated in high-fat diet (HFD)-induced obese mice by using biochemistry and histological analyses as well as by utilizing in vivo settings (ipGTT, ipIST, and body composition). Additionally, to explore the mechanisms of action in the CBD and/or CBG treatment, a metabolomics analysis based on a LC-MS technology was conducted.

Results: The HFD-induced hepatic steatosis, hyperglycemia, and glucose intolerance were significantly attenuated by CBD, CBG, and CBD+CBG. Normalization of HOMA-IR, a marker for β-cell function and insulin resistance, was only found in the HFD-fed mice treated chronically with CBG. Significant improvements in hypercholesterolemia and hypertriglyceridemia were noted in all the treated groups. The above-mentioned findings were not linked to body weight changes. Yet, a significant reduction in fat mass and increased lean mass were found in the CBG-treated mice. Furthermore, liver tissue metabolomics analysis discovered and identified significant metabolites involved in various metabolic pathways, with the sphingolipid metabolic pathways being identified as a potential key player in the mechanism of action by which phytocannabinoids may ameliorate fatty liver disease.

Conclusion: These data indicate that phytocannabinoids, specifically CBD and/or CBG, are potentially able to reverse obesity-related non-alcoholic fatty liver disease. Further efforts to achieve a better understanding of the molecular mechanisms involved are crucial to the development and clinical testing of these phytocannabinoids in humans.

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Renal Mitochondrial ATP Transporter Ablation Ameliorates Obesity-induced Chronic Kidney Disease

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Background: Obesity serves as a risk factor for a wide range of conditions, including the development of chronic kidney disease (CKD). Mitochondrial dysfunction in the renal proximal tubular cells (RPTCs) has been shown to induce kidney injury leading to the development of obesity-induced CKD. However, the underlying molecular mechanisms are not fully understood. Adenine nucleotide translocase 2, which transport ADP and ATP through the mitochondrial inner membrane, plays an essential role in energy metabolism of eukaryotic cells. Here, we explore its specific role in RPTCs in the development of obesity-induced CKD.

Methods: RPTC-ANT2-/- animals were generated using the Cre/loxP system. The null mice and their wildtype littermate controls were fed with either a high fat diet (HFD) or a standard diet (STD) for 24 weeks. For in vitro studies, primary mouse RPTCs were extracted from the null mice and their wildtype littermate controls. Various metabolic and kidney injury parameters were measured in vivo and in vitro using histology, biochemistry and big data omics' analysis.

Results: As evident from the double-stained immunofluorescence staining of mouse kidney, high levels of ANT2 were found in RPTCs. Interestingly, its protein expression was downregulated in HFD-fed WT mice. Nullification of ANT2 specifically in RPTCs prevented the obesity-induced kidney dysfunction as reflected by lowered albumin-to-creatinine ratio, improved renal morphology, reduced renal KIM-1 and NGAL protein levels and downregulation in the expression levels of Mcp1 and Lcn2, markers of renal injury and inflammation, respectively. The null mice were also protected from obesity-induced fibrosis as well as accumulation of triglycerides and cholesterol in the kidney. Unbiased proteome and transcriptome analysis revealed reduced oxidative phosphorylation in absence of RPTC-ANT2, which was confirmed by a decreased pAMPK, CPT1, NAD+ and SIRT1 activity. Lastly, ANT2 depleted primary RPTCs displayed a metabolic shift from fatty acid oxidation-based energy production to aerobic glycolysis, which protected the cells from lipotoxicity-induced damage.

Conclusions: Our findings introduce ANT2 in the RPTCs as a key player in the development of obesity-induced CKD. Deletion of RPTC-ANT2 protects the kidney from the deleterious effects of lipotoxicity. Therefore, targeted manipulation of renal mitochondrial metabolism, particularly via inhibiting ANT2, may represent a novel approach for the treatment of obesity-induced CKD.

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Is leptin resistance in pregnancy a result of the tightening of the blood-brain barrier in the hypothalamus?

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The Arcuate Nucleus (Arc) in the hypothalamus regulates metabolism by direct sensing hormones and metabolites in the bloodstream. Leptin, a hormone secreted by adipocytes, is an anorexigenic hormone that has a crucial role in regulating metabolism. Hypothalamic sensitivity to leptin declines in obesity and during pregnancy and may increase in aging, affecting characteristic weight gain and weight loss in these conditions. However, The mechanism by which leptin enters the Arc is not fully understood. Leptin can enter the Arc through receptors located in endothelial cells or alternatively, through fenestrated blood vessels located in the Median-Eminence (ME), which lies just below the Arc. Fenestrae`s role could be critical in both the transfer of leptin and the development of leptin resistance, as these cellular structures are dynamic and can respond to various physiological conditions.

We show directly using super-resolution microscopy that leptin travels through the fenestrae in the ME. Electron microscopy verified the existence of fenestrated vessels in the ME and surprisingly, also in 25% of the blood vessels in the Arc. These fenestrae provide an alternative route for leptin to reach the Arc without having to pass through the ME. In pregnant mice, fenestrae were virtually lost from endothelial cells in the Arc, providing a mechanism for leptin resistance during pregnancy. In the ME, pregnancy increased the proportion of non-fenestrated blood vessels. We hypothesize that changes in fenestra during pregnancy, aging, and obesity, might affect hormonal flux into the Arc and contribute to the development of leptin resistance.

The role of the Insular Cortex in the anticipatory insulin response

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The human brain has the ability to integrate external and internal signals and create an instantaneous map of the body`s current physiological state, which is essential for maintaining homeostasis and survival. One example of this is the cephalic phase of digestion, which includes a set of anticipatory physiological changes that prepare the body for the imminent intake of food and make its metabolism more efficient. The cephalic phase response can be initiated by the sight, smell, or taste of food. Research has shown that the autonomic parasympathetic system is involved in these responses. However, it is unclear how the brain transforms an external signal of food availability, such as the sight or smell of food, into a coordinated set of physiological changes that include insulin release, salivation, gastric juice release, and more. The mid-posterior part of the insular cortex (InsCtx) has been identified as the "visceral (or interoceptive) cortex" which is able to sense and modulate the body`s functions. Because of these functions as well as its role as a central node in the "salience network" which identifies relevant external cues, we hypothesize that it is also involved in the cephalic phase response. We tested this hypothesis by using chemogenetic inhibition of InsCtx activity, and using cephalic phase insulin release as a measure for the cephalic phase response. Specifically, we used recombinant viral vectors to express Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in InsCtx. Indeed we found that chemogenetic inhibition of InsCtx suppressed the cephalic insulin response. Previous work suggested that the preganglionic brainstem neurons in Dorsal Vagus Complex (DVC) send cholinergic innervation to the pancreas to induce insulin release. We thus used viral circuit mapping techniques to identify candidate pathways from InsCtx to the DVC. We identified two possible pathways - a direct pathway from the InsCtx to the DVC, and an indirect pathway through the Central Amygdala. We are currently using pathway-specific optogenetic activation to selectively activate each pathway and test its role in insulin release and in the cephalic phase response. Disruption of interoception and the cephalic phase response have been linked to various metabolic syndromes such as Type II Diabetes as well as psychiatric disorders including anorexia nervosa, other eating disorders and depression. Understanding the underlying physiological mechanisms will bring us closer to developing therapeutic options to prevent and treat them.

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Diagnosis of Overweight or Obesity and its Association with Performance Rates of Obesity Care in the Primary Care Setting

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Objectives: Obesity has been widely accepted as a chronic medical condition, which requires timely diagnosis, clinical assessment for related complications, intervention and follow up in the primary care setting. However, both overweight and obesity (OW/OB) are underdiagnosed.

The study aim was to assess whether placing a formal diagnosis of OW/OB by the primary care physician for patients with elevated BMI is associated with higher rates of performance of obesity care, and whether OW/OB diagnosis is associated with weight loss compared to missed diagnosis.

Methods: A retrospective cohort study was conducted using Maccabi Healthcare Services database. The study included 200,000 adult patients with a BMI ≥ 25 kg/m2 recorded during a visit at a primary care clinic between January 2014 to December 2020. Patients with prior diagnosis of OW/OB, or obesity-associated complications were excluded. The independent binary variable was having a diagnosis of OW/OB placed by the primary care physician at or immediately after BMI measurement. A composite outcome for performance of obesity management was defined positive if patient was either referred for dietary counseling, bariatric surgery, or prescribed an anti-obesity, and had a second weight measurement within 9-15 months after the first BMI measurement. A second outcome was achieving ≥5% decrease in body weight. The association between OW/OB diagnosis and each of the outcomes was analyzed using a multivariate regression model.

Results: Only 18% of the patients with OW/OB received a diagnosis of OW/OB immediately after their BMI was recorded. Overall, 4.4% were offered clinical care and follow up for their excess body weight, as defined in the composite outcomes. 18.8% had second weight measurement within 9-15M after baseline, of which 20% achieved at least 5% weight loss. In multivariate regression analysis, patients who received a diagnosis of OW/OB were almost two folds more likely to be offered clinical care and follow up for their excess body weight (OR 1.84, p 0.001). Moreover, after adjusting for patient attendance at dietary counseling, patients who received a diagnosis of OW/OB were 32% (OR = 1.32, p0.001) more likely to achieve weight loss of ≥5% compared to patients with OW/OB who were not diagnosed.

Conclusion: OW/OB diagnosis is associated with higher performance of obesity care and an independent predictor of weight loss. Taken together, the high rates of undiagnosed OW/OB present a significant opportunity to improve obesity care and outcomes in the primary care setting.

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The Psychoactive Drug 5-Methoxy-2-aminoindane (MEAI) is a Novel Regulator of Energy Metabolism and Obesity

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Introduction

Obesity and its associated comorbidities represent a growing health challenge worldwide. Currently, there are relatively few effective pharmacological treatments for obesity, and those that do exist have limiting side effects. 5-Methoxy-2-aminoindane (MEAI) is a novel psychoactive aminoindane derivative that exerts a euphoric, alcohol-like tipsy experience, and importantly, reduces the desire to consume alcoholic beverages. Considering these observations, it is also of a great interest to investigate the effects of MEAI on food addictive behaviors. To that end, we tested the metabolic efficacy of MEAI on appetite regulation and obesity.

Methods

To generate diet-induced obesity (DIO), C57Bl6/J adult male mice were fed either a high-fat diet (HFD) or a standard laboratory diet (STD) for 18 weeks. HFD-fed obese mice received vehicle (Saline) or MEAI (40 mg/kg p.o.) daily for 28 days. Age-matched control mice on STD received vehicle daily. Body weight was monitored daily and total body fat and lean masses were determined by EchoMRI-100H™. The metabolic profiles were assessed using the Promethion High-Definition Behavioral Phenotyping System. At the end of treatment, the mice underwent glucose and insulin tolerance testing, and trunk blood and tissues were collected for further biochemical testing.

Results

Treatment with MEAI significantly attenuated the overweight and adiposity associated with obesity in the DIO mouse model, by dually preserving the lean mass, and reducing the overall fat mass. Moreover, HFD-induced hyperglycemia, glucose intolerance, and hyperinsulinemia were reversed by MEAI administration, indicating specific positive effects on glucose metabolism. Additionally, MEAI ameliorated DIO-induced hepatic steatosis by reducing hepatic lipid accumulation and lowering liver triglyceride and cholesterol levels. Metabolic phenotyping revealed that MEAI increased energy expenditure and fat utilization, with a comparable food consumption to that observed in the vehicle-treated group. Lastly, analysis of locomotion patterns indicated that MEAI normalized the reduction in voluntary locomotion actions observed in the vehicle-treated group without having an over-stimulatory effect.

Conclusion

Collectively, these data provide a strong evidence for the anti-obesity effects of MEAI treatment, warranting further preclinical testing.

Discovery and Experimental Confirmation of a Novel Obesity-related Kidney-to-Liver Axis

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Background: Global obesity epidemic affects human health and causes related illnesses, including chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD). Both the liver and kidney are known to regulate whole-body homeostasis. Interestingly, decreased kidney function in settings of liver disease has been previously described as the hepatorenal syndrome; however, the converse clinical problem of hepatic dysfunction in patients with kidney diseases is less recognized. To test the hypothesis whether a metabolic link between kidney and liver exists, we were focused on our newly established mouse model that lacks the mitochondrial ATP/ADP transporter, adenine nucleotide translocase 2 (ANT2), in the renal proximal tubule cells (RPTCs). When fed with a high-fat diet (HFD), these mice were found to be protected from obesity-induced CKD and NAFLD.

Methods: To objectively determine proteins that are related to renal ANT2`s role in liver modulation, we conducted phylogenetics analysis, as well as high-throughput proteomics, biochemistry and pharmacological tests on WT and RPTC-ANT2-/- mice that were fed either a standard diet (STD) or a HFD. Additionally, we verified the presence and activity of the potential protein in serum and kidney samples obtained from both lean and obese humans.

Results: Proteomics analysis revealed that reversal of hepatic steatosis in HFD-fed RPTC-ANT2-/- mice is mediated via increased hepatic SIRT1 signaling, promoting fatty acid oxidation. Utilizing phylogenetics, we discovered that Enpep - which encodes glutamyl/aspartyl aminopeptidase A (APA) - was the gene that co-evolved with ANT2 to the highest degree in the RPTCs. Our results further revealed that in HFD-fed WT mice, the expression and activity levels of APA were significantly upregulated in kidney, liver, and serum samples in comparison to RPTC-ANT2-/- animals. In addition, we found that obese individuals had higher levels of circulating and renal APA expression and activity, which were positively correlated with the extent of liver damage in these patients. Finally, treatment with Amastatin (3 mg/kg/day, i.p.), a non- specific APA blocker, in HFD-fed obese WT mice led to improved energy utilization, decreased glucose intolerance and insulin resistance, and ameliorated liver injury and steatosis.

Conclusions: These findings clearly support the metabolic role APA has in the context of obesity and its related illnesses. In addition, they provide a new understanding related to the effect of kidney-derived molecules on liver function in settings of obesity; and, may add novel information regarding the therapeutic potential of drugs targeting APA for treating the metabolic syndrome and NAFLD.

Circulating “Inflammo-miRNAs”: a “liquid biopsy” approach to detect human obesity phenotypes with high versus low visceral adipose tissue inflammation

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Background: The extent of visceral adipose tissue (VAT) inflammation in individuals with obesity is thought to signify obesity sub-phenotypes that differently associate with increased cardiometabolic risk. Yet, while assessing VAT inflammation may assist in patients’ risk stratification/classification, this tissue is not accessible for direct sampling in the non-surgical patient. Moreover, there is no universally accepted clinical approach to evaluated VAT-inflammation. We hypothesized that circulating miRNAs could serve as clinically-accessible biomarkers for estimating the degree of obesity-associated VAT-inflammation.

Methods: Patients with obesity undergoing elective abdominal surgery (n=35, median BMI=40.0 kg/m2) were classified into high/low VAT inflammation (14[47%]/16[53%]), respectively), based on an expression score derived from the mRNA levels of TNFA, IL6 and CCL2 (determined by rtPCR; n=5 had intermediate score and were excluded to decrease misclassification bias). A clinical estimation of the degree of VAT inflammation was conducted independently by 2 endocrinologists, who were blinded to the laboratory evaluation, based on clinical (e.g., age, the presence of diabetes) and biochemical (e.g., triglyceride level) data. Circulating miRNAs were sequenced by NGS, and differentially-expressed miRNAs were identified using several complimentary methods: Mann-Whitney, Deseq2 and ROC-AUC analyses. We further scrutinized the discriminative power of putative circulating “VAT-inflammomiRs” by Leave One Out (LOO) prediction approach.

Results: Although patients with high VAT-inflammation did not differ in their clinical characteristics, they trended to exhibit greater degree of insulin resistance (Fasting insulin and HOMA-IR of 18.6±8.2 vs 11.9±13.1; 4.6±1.6 vs 2.8±3.2, respectively, both p=0.061). Importantly, no patient had known cardiovascular disease at the time of the abdominal surgery. The combined clinical assessment poorly predicted VAT-inflammation with an accuracy of 0.433 and True Positive Rate of 0.429. Fifty four out of 263 circulating miRNAs (20%) associated with high VAT inflammation according to Mann Whitney analysis. Of those, 13 (13/54=24%) were differentially expressed according to Deseq2 and 7 significantly discriminated between high and low VAT-inflammation with ROC-AUC0.8. Of resulting 5 circulating miRNAs that were differentially abundant in high/low VAT-inflammation plasma, the combination of hsa-miR-181b-5p and hsa-miR-423-5p and patient’s age exhibited exceptional discriminative power, with ROC-AUC of 0.96(0.91-1.0). LOO prediction analysis showed an accuracy of 0.833, with True Positive Rate of 0.86. Predicted target genes of these miRNAs exhibit enrichment of insulin regulation and inflammatory pathways.

Conclusions: A clinical calculator based on plasma-levels of miRNAs 181b-5p and 423-5p and age can improve clinicians’ ability to stratify patients to obesity with either low/high VAT-inflammation and inspire more personalized obesity management.

Novel Peripherally Restricted Cannabinoid-1 Receptor Blockers for Treating Diet-induced Obesity and its Metabolic Complications

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Introduction: Cannabinoid-1 receptor (CB1R) antagonists have been shown to reduce body weight, increase energy expenditure, and improve the metabolic abnormalities associated with obesity in preclinical models and humans. However, neuropsychiatric side effects (such as depression, anxiety, and suicidal ideation) mediated by brain-penetrating compounds limited their therapeutic potential. Several lines of evidence suggest that activation of the peripheral endocannabinoid/CB1R system contributes to diet-induced obesity (DIO) and its metabolic consequences. This indicates that CB1R blockade in the periphery could serve as a proper treatment for DIO while sparing CNS-mediated adverse effects. Here, we describe the synthesis and metabolic evaluation of a series of peripherally-restricted CB1R blockers.

Methods: A library of 28 compounds (BNS801 through BNS828) was synthesized by chemically linking different moieties to the core structure of 5,6,7,8-tetrahydrooxepino[3,2-c]pyrazol-8-amine, predicted to have reduced CNS exposure. CB1R binding, activity, and selectivity against CB2R were assessed. In addition, the potential brain penetration of selected compounds was evaluated using a bi-directional permeability study across MDR1-MDCKII cells, with and without a P-glycoprotein (P-gp) inhibitor. The efficacy of selected lead compounds in ameliorating obesity and its metabolic complications in DIO mice, including glucose homeostasis, dyslipidemia, hepatic injury, and steatosis, were determined.

Results: Several vital compounds demonstrated promising CB1R antagonism, having Ki values in the nanomolar range and low CB2R affinity. We identify BNS808 and BNS822 as highly potent and selective CB1R antagonists, exhibiting Ki values of 0.6 nM and 1.3 nM, respectively. In addition, BNS808 was found to have a relatively high efflux ratio and is suspected to be a P-gp substrate in the MDR1-MDCKII permeability assay, predicting its reduced CNS exposure. Finally, chronic oral administration of BNS808 (1 mg/kg/day, for 21 days) and BNS822 (20 mg/kg/day for 21 days) significantly reduced body weight, improved the metabolic profile, and alleviated hepatic steatosis in DIO mice.

Conclusions: Our results demonstrate the synthesis and rapid in vitro evaluation of a new library of potentially peripheral CB1R blockers. This library could be further optimized to identify additional peripherally targeted CB1R antagonists. Two compounds were identified as highly potent and selective peripheral CB1R blockers; BNS808 and BNS822 demonstrated encouraging safety and efficacy in treating obesity and its metabolic abnormalities.

Inherited Stress Resiliency Prevents the Development of Metabolic Alterations in Diet-Induced Obese Mice

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Introduction: Obesity represents a significant risk for development of cardio-metabolic diseases, and is associated with increased mortality. However, whereas most overweight individuals are metabolically unhealthy (metabolically unhealthy obese, MUO), a minority are relatively healthy (metabolically healthy obese, MHO) The exact mechanisms affecting the health of obese subjects have not yet been discovered. Objective: To clarify whether differences in stress response affect metabolic health, and to search for underlying mechanisms. Methods: The study was performed in a selectively-bred mouse model of inherited social dominance (Dom) and submissiveness (Sub) which exhibit stress resilience or vulnerability, respectively. Mice were given high fat diet (HFD) or standard diet (STD), followed by physiological, histological and molecular analyses. Results: Obesity was developed in both groups, however HFD-feeding induced hyperleptinemia as well as severe glucose intolerance and insulin resistance in Sub mice, while Dom mice were almost unaffected. Histochemistry analysis revealed pancreatic islets hypertrophy and steatosis in Sub, while these pathologies were absent in Dom mice. Furthermore, steatosis was observed in liver and in intercapsular BAT (iBAT) of Sub, while Dom mice were protected from these consequences of HFD feeding. Additionally, white adipose tissue browning was documented based on histological staining, protein and gene expression of thermogenic genes, in Dom but not in Sub mice. The presence of inflammation, and the role of this pathology in the metabolic alterations developed in Sub mice, was investigated as well. HFDinduced the expression of pro-inflammatory genes in the liver and in epididymal white adipose tissue (eWAT) of Sub mice, while Dom mice were protected from these effects of HFD feeding. Moreover, pro-inflammatory genes were elevated in inguinal WAT (iWAT) of Sub mice even under regimen of STD feeding, suggesting fundamental tissue impairment. In order to find whether inflammation is involved in the metabolic alterations observed in obese Sub mice, Sub and Dom mice were given HFD feeding in the presence or absence of an anti-inflammatory agent (celecoxib, a Cox2 inhibitor). Celecoxib improved glucose tolerance and insulin sensitivity and prevented hepatic and BAT steatosis in HFD-fed Sub mice, while Dom mice were unaffected. In addition, expression of pro-inflammatory markers was modified by celecoxib in adipose tissue of Sub mice. Similarly, serum IL1beta levels were reduced by Celecoxib in HFD-fed Sub mice. Conclusions: Stress vulnerability, accompanied by an elevated inflammatory state, contribute to higher susceptibility to metabolic alterations.

Weight Regain Following Bariatric Surgery and In Vitro Fertilization Outcomes

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Background: Studies have suggested a positive influence of bariatric surgery (BS) on in vitro fertilization (IVF) outcomes. However, information on the effect of weight regain post-BS on IVF outcomes is scarce.

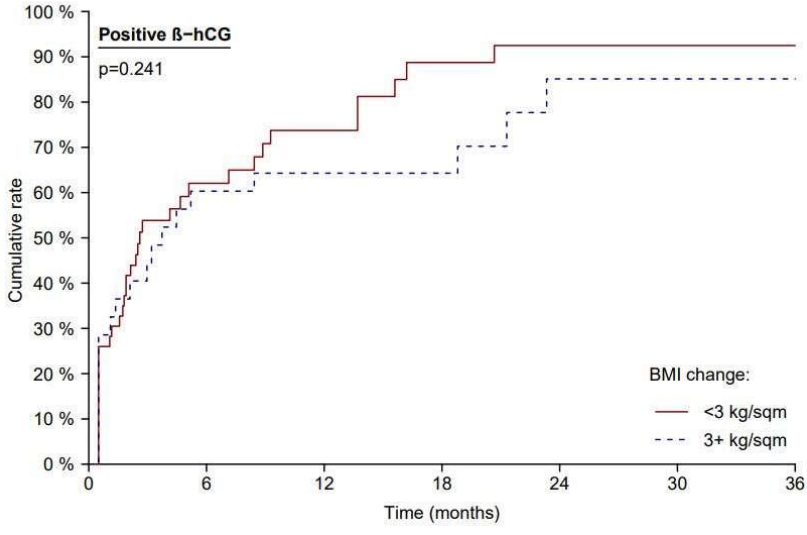
Objective: To estimate time to pregnancy and live birth and to evaluate the effect of weight regain among women with a history of bariatric surgery (BS) who underwent in vitro fertilization (IVF) treatments.

Material and Methods: Historical cohort study. All female patients who had previous BS and underwent IVF treatments and were treated in Sheba Medical Center from 2013 and 2022 were included. Time to pregnancy and live birth was evaluated for all patients. Then, time to pregnancy and live birth was compared between patients who regained less than and greater than three units of body mass index (BMI), from their nadir weight after surgery (approximately five kg). Kaplan-Meier curve was used to describe time to positive β-hCG, clinical pregnancy, and live birth. Kaplan Meier curve and log-rank tests were used to compare time to positive β-hCG, clinical pregnancy and live birth among the two groups of weight regain.

Results: A total of 78 patients were included. Positive β-hCG, clinical pregnancy and live birth rates following bariatric surgery were 89.4%, 78.9% and 50.8%, respectively. The median time from the beginning of IVF treatments to a positive β-hCG test was 2.97 months (95%CI 1.04-4.89 months), to a clinical pregnancy was 7.1 months (95%CI 3.56-10.91) and to a live birth was 20.2 months.

Women who maintained their nadir BMI following bariatric surgery, had nearly twice the chance to achieve a clinical pregnancy (HR 1.894, 95%CI 1.012-3.545, p=0.046), and were approximately three times more likely to achieve a live birth (HR 2.931, 95%CI 1.261-6.810, p=0.012), compared to those who regained at least three units of BMI.

Conclusion: Weight regain of more than three units of BMI from the nadir BMI after BS is associated with a lower rate of live birth and a prolonged time to achieve clinical pregnancy and live birth. Women who have undergone BS and who have not achieved pregnancy by 24 months of IVF treatments have significantly low chance of becoming pregnant with continued treatment.



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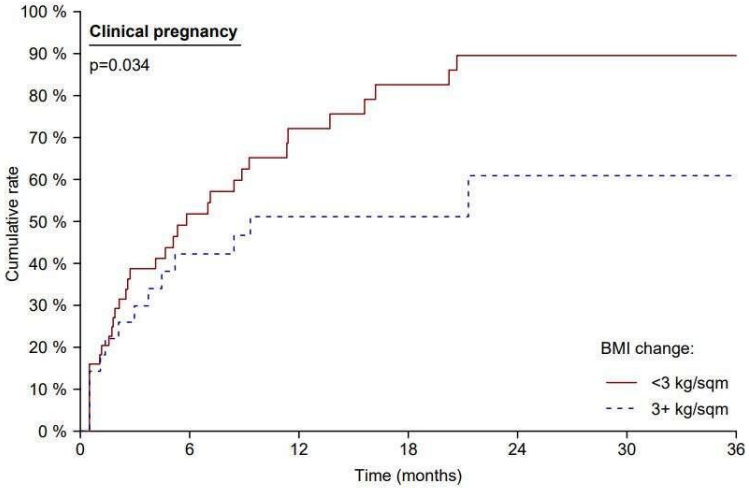
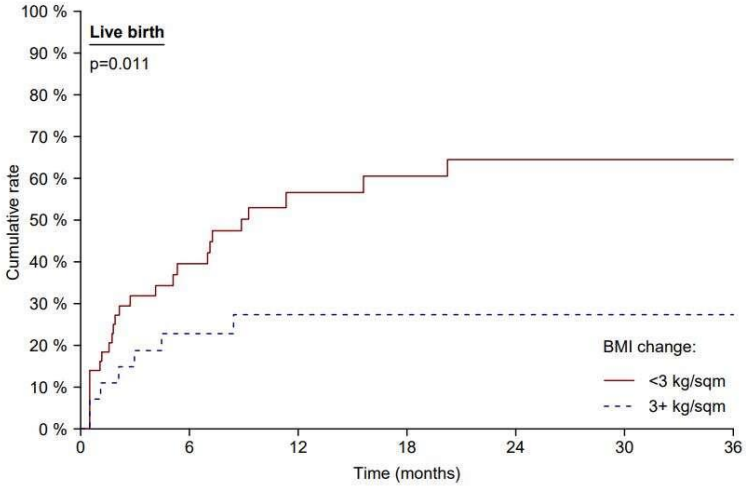

Clinical pregnancy
p=0.034
Cumulative rate
100 %
90 %
80 %
70 %
60 %
50 %
40 %
30 %
20 %
10 %
0 %
0
6
12
18
24
30
36
Time (months)
BMI change:
<3 kg/sqm
3+ kg/sqm


Live birth
p=0.011
Cumulative rate
100 %
90 %
80 %
70 %
60 %
50 %
40 %
30 %
20 %
10 %
0 %
0
6
12
18
24
30
36
Time (months)
BMI change:
<3 kg/sqm
3+ kg/sqm

290

Predictive value of ovarian reserve parameters for follicle detection in ovarian tissue cryopreservation

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Introduction: In youth, primary ovarian insufficiency (POI) is due to genetic, autoimmune, iatrogenic, and idiopathic etiologies. When POI is diagnosed early with evidence of an ovarian reserve, fertility preservation can be offered. When the girl is premenarchal, the preferred fertility preservation method is ovarian tissue cryopreservation (OTC) containing primordial follicles. In the past, when OTC was performed in an unselected group of children and adolescents with Turner syndrome, only 25% had follicles in ovarian tissue.

Aims: To evaluate the yield of ovarian reserve parameters as predictors of OTC outcomes in girls suffering from non-iatrogenic POI, to avoid unnecessary invasive procedures.

Methods: We retrospectively assessed the ovarian reserve parameters of girls ≤ 18 years with non-iatrogenic POI who were referred for fertility preservation counseling in one tertiary center during the years 2010-2020. OTC was recommended if at least one positive parameter suggesting ovarian activity was present. A positive parameter was defined as anti-Mullerian hormone (AMH) 0.16ng/ml, follicle-stimulating hormone (FSH) ≤ 20mIU/ml, or detection of ≥ 1 antral follicle by transabdominal sonography. Patients with 46XY gonadal dysgenesis were excluded.

Results: The cohort included 37 patients (27 Turner syndrome, 6 idiopathic POI, 3 Galactosemia, and one Blepharophimosis, Ptosis, and Epicanthus Inversus syndrome). Sixteen patients underwent OTC, at a mean age of 14.2±3.1 years. Among the group who underwent OTC, compared to the group who did not have OTC, FSH was lower (29.0±31.7 vs. 53.4±52.6 mIU/ml, p=0.05), and the proportion of measurable AMH was higher (50% vs. 15%, p=0.03). The proportion of Turner patients was 1.5-fold lower among the patients who underwent OTC compared to those who did not have OTC (56% vs. 88%, p=0.02). Among the group who underwent OTC, follicles were detected among 79% of the patients, and in all patients (100%) who had 2 or 3 positive parameters. The median number of follicles was 2.5 (range 0-75) in patients who had ≥1 positive parameter, and 22.5 (range 13-64) in patients with 2-3 positive parameters.

Conclusion: This study shows that if OTC is performed in patients with ≥1 positive parameter of ovarian activity, a 79% positive predictive value is achieved for the detection of follicles. The incorporation of these criteria will improve the success rate of OTC as a fertility preservation procedure in these patients and minimize the risk of harvesting ovarian tissue with a low number of follicles.

Sublingual Estradiol Offers no Advantage Over Combined Oral Estradiol and Cyproterone Acetate for Gender Affirming Hormone Therapy of Treatment-Naïve Transwomen: Results of a Prospective Pilot Study.

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Background: The standard approach for Gender-Affirming Hormone Therapy (GAHT) of transgender women (TW) in Israel is oral estradiol (OE) combined with the potent anti-androgen cyproterone acetate (CA). Recently, many of our non-binary patients have requested sublingual estradiol (SLE) without CA, under the unproven belief it preserves erectile function, and does not induce depression. Preliminary data in a few subjects, who self-practiced this approach, suggested it also maintained higher testosterone levels.

Hypothesis: By not suppressing testosterone (T) as profoundly, SLE should be less detrimental to sexual function, and might be superior to OE for improving dysphoria.

Study design: A 6 months controlled, unblinded and non-randomized, prospective study of treatment-naïve TW seeking GAHT.

Patients and Methods: 22 healthy, treatment-naive TW. The SLE arm consisted of 0.5 mg of estradiol 4 times a day, while the OE consisted of oral 2 mg estradiol together with 10 mg CA once daily. Subjects underwent exhaustive chemical, hematologic and hormonal laboratory assessments, and body composition analysis at baseline and after 6 months. Furthermore, they completed validated dysphoria, sexual desire and function questionnaires.

Results: At baseline, the only difference between the groups was age. Subjects who chose SLE, were older 26.3±5.8, vs. 20.1±2.3 yr for OE (P=0.006). Baseline testosterone 19.5±6.8 nmol/L; estradiol 113.3±32.7 pmol/L; LH 4.3±1.4 IU/L; FSH 4.5±3.4 IU/L; and prolactin 226±150 mIU/L were identical between the groups.

By paired comparisons, GAHT generated significant, and expected changes at 6 months in both groups: creatinine, hemoglobin, hematocrit, total and LDL cholesterol, testosterone, gonadotropins all decreased, while estradiol and prolactin rose. BMI remained unchanged, but there was a significant increase in fat mass, and a decrease in lean body mass in both groups. At 6 months, the only differences between the treatment groups were higher estradiol, and LH in the SLE group: 204.6±63.3 vs. 109.7±53 pmol/L, P=0.02; and 3.5±1.2 vs. 1.6±1.3 IU/L, P=0.007, respectively.

Median estradiol, 90 minutes after 0.5 mg SLE was 1721 [IQR 1000-2432] pmol/L. Remarkably, dysphoria did not improve in either group during the study period. Sexual desire and function decreased significantly with both treatments, and were not spared by the SLE protocol.

Conclusions: GAHT of TW with SLE over 6 months, offers no clear advantage over the standard OE approach that includes CA, neither in hormonal, biochemical and body composition variables, while it generates recurring supraphysiological estradiol concentrations throughout the day, the safety of which, particularly with respect to thrombogenicity, remains to be determined.

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Serum Adropin is Reduced in Post-Menopausal Women

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Intro: Adropin is a hepatokine with beneficial cardio-metabolic effects on energy metabolism and vasculature function. Reduced serum adropin is associated with various adverse cardio-metabolic phenotypes. We were the first to report that hepatic adropin expression is reduced in ovariectomized (OVX) female mice and that it is directly regulated by estrogen (J. Stokar et al. Molecular Metabolism 2022; PMID: 35364299). Thus, adropin is a potentially relevant biomarker for cardiometabolic health in peri and post-menopausal women. **Methods**: To extend our results to humans, frozen serum samples of healthy women between the ages of 40-60 years were obtained from the Central BioHub repository. 17-β-estradiol (E2) and follicle stimulating hormone (FSH) were measured automatically using electro chemiluminescence immunoassay (Cobas; Roche). Adropin levels were measured in duplicates using an enzyme immunoassay (Phoenix pharmaceuticals #EK-032-35). Post-menopausal status was determined by 17-β-estradiol (138.00 pg/ml) with concomitant high FSH (25.80 mIU/ml). **Results**: a total of 32 samples were obtained. Using E2 and FSH criteria, 14 women were defined as pre-menopausal (mean age 46.2 ±4.4) and 18 as post-menopausal (mean age 51.5 ±4.1). Intra and inter-assay CV% for serum adropin was 9% and 14% respectively. Mean serum adropin was significantly lower in post-vs pre-menopausal women (0.93 vs 1.32 ng/ml p=0.03). Serum adropin was not correlated with E2 level but did trend towards an inverse correlation with FSH (Pearson's R=-0.34 p=0.07) as well as with age (R=-0.32 p=0.06). **Conclusions**: serum adropin is reduced in post-vs-pre-menopausal women. Reduced serum adropin may play a role in adverse cardio-metabolic phenotypes associated with menopause. Further studies are warranted to examine serum adropin as a potential cardio-metabolic biomarker in the peri and post-menopausal states.

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Is there seasonal variation in testosterone levels? Data from a large cohort of men

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Context: Various data suggest seasonal variation in testosterone levels. However, previous studies are limited by either small sample size or by variability in baseline characteristics and confounders, such as differences in age and weight distribution, co-existent illness, time in the day in which testosterone was measured and by differences in geographic location and climate conditions. Ultraviolet (UV) exposure is one of the main environmental stimuli. In a recent study , we explored a novel skin-brain-gonad axis triggered by UV and mediated by skin p53. Through the use of various mouse models, we found that UV exposure led in male and female mice to increased hypothalamus-pituitary-gonadal axis hormone levels and to increased sexual responsiveness and attractiveness.These data provide for the first time an underlying mechanism for seasonal variability in testosterone levels.

Objectives: The aim of the study was to evaluate in a large cohort of males with a wide range of age, metabolic status, and coexistent morbidities whether month of blood test performance was associated with

total and bioavailable testosterone levels independent of age, body mass index (BMI), existing cardiovascular disease (CVD), and CVD risk factors.

Methods: Cross-sectional study includes data from computerized medical records of 27,328 men aged 20–70, treated by the largest healthcare organization in Israel, who had undergone testosterone measurement. In 7,940 subjects with available sex hormone-binding globulin levels, bioavailable testosterone was calculated.

Results: Total and bioavailable testosterone levels gradually decreased with age and BMI (P 0.001) and were significantly lower in men with diabetes, hypertension, hyperlipidemia, and known CVD, but were higher in current smokers compared with nonsmokers (P 0.001). Hormone levels were highest in August-October declined after and lowest in March. Overall, both total and bioavailable testosterone levels were significantly lower in March compared to August-October (P 0.001). In a linear regression analysis, age, BMI, current smoking, and month of testing were independently associated with both total (P 0.001) and bioavailable testosterone levels (P 0.002), and diabetes was associated with total testosterone (P 0.001).

Conclusion: In a large cohort of men with a wide range of age, BMI, and comorbidities, month of testing was independently associated with total and bioavailable testosterone levels. These data provide strong evidence that seasonal variation has to be considered in clinical practice especially in men with borderline levels.

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Body composition in children and adolescents with non-classic congenital adrenal hyperplasia and the risk for components of metabolic syndrome: An observational study

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Background: Treated or untreated non-classic congenital adrenal hyperplasia (NCCAH) diagnosed in childhood could pose an increased risk of obesity and metabolic derangements in adolescence and early adulthood. We aimed to explore the interaction between muscle-to-fat ratio (MFR) and components of metabolic syndrome in pediatric subjects with NCCAH.

Methods: This retrospective observational study was conducted in the Tel Aviv Medical Center from January 2018 to January 2022. The study group comprised 75 subjects (26 males) with NCCAH (61 hydrocortisone-treated [21 males] and 14 untreated [5 males]) and 134 healthy sex- and age-matched subjects (41 males) with normal puberty served as controls. Body composition was measured by bioelectrical impedance analysis (BIA) and muscle-to-fat ratio (MFR) z-scores were calculated. Stepwise linear regression models were applied to evaluate explanatory variables for MFR z-scores, blood pressure percentiles, lipid profiles, and glucose metabolism.

Results: The median age [interquartile range] was 7.5 years [5.3, 8.8] at NCCAH diagnosis and 12.3 years [8.9, 15.4] at BIA. The median cumulative hydrocortisone dose was 7620 mg/m2 [2547, 12903]. Subjects with NCCAH had higher mean BMI z-scores and lower median MFR z-scores compared to controls [(0.47 ± 0.97 vs. -0.19 ± 1.04, p0.001) and (-0.74 [-1.06, -0.14] vs.-0.37 [-0.99, 0.15], p=0.045), respectively]. The linear regression models dependent variables and their explanatory variables were: MFR z-score (R2= 0.253, p0.001) - socioeconomic position index (β=0.348, p=0.003), birthweight z-score (β=-0.258, p=0.013), and duration of hydrocortisone treatment in years (β=0.048, p=0.023); systolic blood pressure percentile (R2 = 0.166, p0.001) - MFR z-score (β=-9.75, p0.001); TG/HDL ratio (R2 = 0.116, p=0.024) - MFR z-score (β=-0.300, p=0.024). No significant variables were found for glucose.

Conclusions: Children and adolescents with NCCAH have a body composition characterized by an imbalance between muscle and fat tissues, which may place them at increased risk for early-onset cardiometabolic derangements. It is reassuring that glucocorticoid therapy aimed to alleviate androgen overproduction does not appear to adversely affect their body composition.

Genotype-Specific Cortisol Reserve in a Large Cohort of Subjects with Non-Classic Congenital Adrenal Hyperplasia (NCCAH)

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Background: Recent guidelines suggest that NCCAH subjects stop their glucocorticoid therapy after achieving adult height. However, these guidelines do not refer to the different genotype groups within the NCCAH population.

Aim: To compare ACTH stimulated cortisol and 17-hydroxyprogesterone (17OHP) levels, and the rate of partial cortisol insufficiency, between NCCAH subjects carrying one mild and one severe mutation (mild/severe) to those with bi-allelic mild (mild/mild) mutations.

Methods: Subjects with postnatal virilization (mainly precocious adrenarche) underwent the standard intravenous 0.25 mg/m² ACTH stimulation test. Those with stimulated 17OHP level above 40 nmol/L were screened for the nine most frequent CYP21A2 gene mutations followed by Multiplex Ligation-dependent Probe Amplification (MLPA). Stimulated cortisol levels below 500 nmol/L were considered as an insufficient cortisol reserve.

Results: NCCAH subjects (n=119) were subdivided according to their genotype to three groups: 77 carried the mild/mild genotype, mainly homozygous for p.Val282Leu mutation; 29 were compound heterozygous for one mild and one severe mutation, mainly p.Val282Leu/ p. I2Splice and 13 were heterozygous for p.Val282Leu, and therefore were excluded from the statistical evaluation.
Stimulated cortisol levels were significantly lower in the mild/severe compared to the mild/mild group (mean±sd, 480±90 vs 570±125 nmol/L, p0.001). The mild/severe group exhibited a significantly higher rate of partial cortisol insufficiency (21/28, 75% vs 28/71, 39%, p= 0.004). Peak 17OHP was significantly higher in the mild/severe group (198±92 vs 118±50 nmol/L, p0.001) with a suggested cut-off level of 170 nmol/L to distinguish between the genotype groups.

Conclusions: The high rate of partial adrenal insufficiency in the mild/severe group suggests a special consideration regarding glucocorticoid therapy cessation and the need for stress coverage in this group.

A 120-Minute Saline Infusion Test for the Confirmation of Primary Aldosteronism

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Objective: Saline infusion test (SIT) for confirmation of primary aldosteronism (PA) traditionally requires two liters of normal saline and is 240 minutes long. Previous studies have raised concerns regarding increased blood pressure (BP) and worsening hypokalemia during and after SIT. Therefore, we aim to evaluate the diagnostic applicability of a shorter, one liter 120-minute-long SIT.

Design and Methods: A cross-sectional study, including all consecutive patients with suspected PA who underwent SIT from 1st January 2015 to 31st December 2022 in a large, tertiary medical center in Israel. Blood samples were drawn for renin and aldosterone at baseline (t=0), after 2 hours (t=120 min), and after 4 hours (t=240 min) of saline infusion. Receiver-operator curve (ROC) analysis was used to evaluate the sensitivity and specificity of various aldosterone cutoff values at t=120 for the confirmation of PA. Logistic regression was performed to analyze the association of baseline variables and aldosterone levels after 120 minutes and after 240 minutes.

Results: The final analysis included 55 patients. ROC analysis with an area under the curve (AUC) of 0.97 (95% CI [0.93, 1.00], P 0.001) demonstrated 90% specificity and 92% sensitivity for an aldosterone cutoff value of 342 pmol/L at t=120 to confirm PA. 45% (25/55) of patients did not suppress aldosterone levels after 240 minutes, of them 92% (23/25) did not suppress aldosterone at t=120 according to the 342 pmol/L cutoff. Univariate analysis showed that male sex, hypokalemia, and elevated systolic BP were all associated with failure to suppress aldosterone levels below the traditional threshold for PA confirmation at t=240 (i.e.

Conclusions: We present data showing that an aldosterone cutoff of 342 pmol/l at t=120 has both high sensitivity and specificity for PA diagnosis confirmation.

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Hyperglycemia-Induced Unique Transcriptional Changes in Osteocytes

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Introduction: Diabetes leads to skeletal fragility and an increased fracture risk. As a master regulator of bone-remodeling, osteocyte dysfunction may play a role in the pathogenesis of diabetes-related skeletal fragility. To study the effects of hyperglycemia on the osteocyte in-isolation, we used the osteocyte-like cell line IDG-SW3 taking an unbiased multi-omics-based approach. **Methods:** IDG-SW3 cells were plated in a differentiation osteogenic medium under 3-conditions: normal glucose (5mM; NG), high-glucose (25mM; HG) and mannitol 20mM with glucose 5mM to control for the hyperosmolarity induced by HG. Media was changed twice weekly for 28 days, with cells harvested at 1,3,7,14, 21 and 28-days post differentiation induction. 3-biological-replicates were used for each condition with the entire experiment repeated 3-times. RNA was extracted from cell lysates 14 days after induction to osteogenesis with bulk RNA-SEQ performed. Protein was extracted at day 16 after induction to osteogenesis with proteomics analysis by LCMS. **Results:** HG conditions led to lower PH in the supernatant and a delay in markers of osteocyte differentiation. RNA-SEQ analysis revealed 1340 differently expressed genes (767 up 573 down; DEGs). Interestingly, mannitol led to a much smaller transcriptional change with only 103 DEGS vs NG (cut-off of FC2 and p.adj 0.05) with just 38 DEGs in common between the comparisons. Ingenuity Pathway Anaylsis (IPA) of DEGs (HG vs NG) revealed significant deactivation of the autophagy related pathways CLEAR Signaling (Z-score -3.015, -log[B-H p-value] 8.31) and Phagosome Formation (Z-score -3.43, -log[B-H p-value] 1.458); a pattern not observed in mannitol vs NG. Proteomics analysis revealed HG led to activation of the senescence pathway (Z-score 1.213 -log[B-H p-value] 3.66) and deactivation of the CLEAR signaling pathway Z-score -0.755 -log[B-H p-value] 3.03). **Conclusion:** These results reveal the differential effects of hyperosmolarity and hyperglycemia on transcriptional changes and cell differentiation in the osteocyte, which may play a role in the pathophysiology of diabetes-related skeletal fragility. Specifically, the deactivation of autophagy and activation of senescence pathways induced by hyperglycemia in osteocytes warrant future research, as they may serve potential therapeutic targets for prevention and treatment of diabetes-related skeletal fragility.

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Burosumab therapy in children with X-linked hypophosphatemia: a real-life long-term study

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Background: Burosumab was approved for treatment of X-linked hypophosphatemia (XLH) as monotherapy in 2018. we aimed to evaluate the long-term effectiveness of Burosumab for children with XLH in a real-life clinical practice.

Methods: This retrospective multi-center real-life study included 35 pediatric patients who initiated Burosumab treatment between January 2018 to January 2021. We retrieved clinical data, anthropometric measurements, laboratory results and rickets severity score (RSS) for the period beginning at two years prior to Burosumab initiation till up to four years later.

Results: Burosumab treatment was initiated at mean age of 7.5±4.4 years (range 0.6 - 15.9 years). The mean initial dose was 0.8±0.3 mg/kg and it was increased up to 1.1±0.4 mg/kg. The followed-up duration was 2.9±1.4 years (range 1-4 years) after Burosumab initiation. During Burosumab treatment serum phosphorus levels increased significantly from 2.7±0.8 mg/dl at Burosumab initiation to 3.4±0.6 mg/dl after three months, and remained stable (p0.001). Alkaline phosphatase level decreased statistically significant, while 1,25 dihydroxy vitamin D and total reabsorption of phosphorus increased significantly. RSS improved from 1.7±1.0 at burosumab initiation to 0.5±0.6 and 0.3±0.6 at 12 and 24 months later (p0.001). height Z-score and weight Z-score improved between burosumab initiation and the end of the study: -2.07±1.05 versus -1.72±1.04 (p0.001), and -0.51±1.12 versus -0.11±1.29, respectively. Eight children were treated with growth hormone during the study period. Improvement in height Z-score was statistically significant both in those treated and not treated with growth hormone.

Conclusion: Burosumab treatment in a real-life setting was effective to improve phosphate homeostasis, rickets and growth.

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The association between antiresorptive therapy, fracture risk and mortality in osteoporotic patients with concurrent type II diabetes mellitus: a large, population-based cohort study.

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Background: Despite having higher bone mineral densities (BMD), patients with type II diabetes mellitus (TIIDM) are at an increased risk of fracture. Anti-resorptive therapies are the mainstay of osteoporosis (OP) management, however, evidence of their efficacy in the TIIDM population is limited.

Aim: To assess the association between anti-resorptive treatment and the risk of major osteoporotic fracture (MOF) and all-cause mortality in osteoporotic patients with TIIDM.

Methods: A population-based cohort in a large state-mandated health fund in Israel including patients with OP and TIIDM was conducted. We extracted patient demographic data, DM history, OP history and presence of comorbidities known to increase fracture risk. Demographic data were expressed as means ± standard deviation and differences were analyzed using student's t-test and chi2. Standardized fracture risks were assessed using the Cox proportional hazard model.

Results: Our cohort consisted of 27503 diabetic and osteoporotic patients, 68% were female. The mean follow up was 10.6±9.8 years. The mean age at DM diagnosis was 65.8±8.8 years and mean age at OP diagnosis was 71.38±9.54 years, with a mean duration of diabetes of 6.9±5.4 years, and a mean HbA1c of 6.8±0.8 at OP registry entry. The mean BMI was 29.3±5.5, mean FN BMD T-score -1.8±1.2, HIP BMD T-score -1.3±3.3, and LS BMD T-score -1.2±1.6. The Charlson Comorbitity Index (CCI) was 3.6± 2.5.

A total 13343 (45.5%) patients received anti-resorptive treatment; 30.2% were treated with alendronic acid, 14.3% with risedronic acid, 2.3% with zoledronic acid and 1.8% with denosumab. A total of 14719 (46.4%) patients sustained a MOF, 62.5% non-treated patients versus 37.5% treated patients (p0.001). A multivariate analysis showed a significant fracture risk reduction in treated patients HR 0.495 (0.477-0.514, P0.001) after adjustment for age, BMI, BMD, CCI, HbA1c levels, duration of diabetes and insulin treatment. There was also a significant reduction in all-cause mortality (HR 0.679, 0.586-0787) and cardiovascular events (HR 0.824, 0.755-0.900) in patients with HbA1c under 8%.

Conclusions: Our data suggests that anti-resorptive treatment significantly reduces the incidence of major osteoporotic fractures in diabetic patients, independently of HbA1c levels and diabetes duration. It was associated with a significant reduction in cardiovascular events and mortality in patients with HbA1c under 8%.

Distinct Growth Characteristics in Angelman Syndrome

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Objectives: Angelman syndrome (AS) is a rare, genetic, neurodevelopmental disorder characterized by severe impairments in speech, cognition and motor skills accompanied by unique behaviors, distinct facial features and high prevalence of epilepsy and sleep problems. Despite some reports of short stature among AS patients, this feature is not included in the clinical criteria defined in 2005. We investigated growth patterns among AS patients with respect to mutation type, growth periods, family history and endocrine abnormalities.

Methods - Data regarding growth and puberty of patients and their parents were collected from medical files of AS patients in the national AS clinic. The cohort was divided into two subgroups – deletion and non-deletion. Growth data was divided to four main periods – preschool, childhood, peak height velocity and final height.

Results – The cohort included 88 individuals (46 males), out of which 54 (61.4%) had the deletion subtype. There was a median of 3 observations per individual (range 1-10), which produced 280 data points distributed from birth to final height. Mean final height-SDS of the cohort was significantly lower compared to the general population (-1.23 ±1.26, p0.001), and among the deletion subgroup it was significantly lower compared to the non-deletion subgroup (-1.67±1.3 vs -0.65±0.96, p=0.03). Final height-SDS was significantly lower compared to height SDS in preschool period (-1.32 vs -0.47, p=0.007). Patient`s final-height-SDS was significantly lower than the parents` (Δfinal-height-SDS=0.94±0.99, p=0.002). IGF1-SDS was significantly decreased compared to the general population (-0.55±1.61, p=0.04), with lower values among the deletion group (-0.70±1.44, p=0.01). IGF1 was positively correlated with height-SDS (r=0.65, p=0.007). No significant changes were seen in timing of puberty.

Conclusions -AS patients demonstrate a unique growth pattern, with deceleration throughout life up to a significantly decrease in final height compared to the normal population, and even lower among the deletion subgroup, which could be attributed to decreased IGF1 levels. We propose to add short stature to the clinical criteria and develop adjusted growth curves for the AS population.

Key word - Angelman syndrome, growth curves, short stature, height, weight, deletion, non-deletion, IGF1.

Novel Calcium-Sensing Receptor (CASR) Mutation in a Family with Autosomal Dominant Hypocalcemia Type 1 (ADH1): Genetic Study over Three Generations and Clinical Characteristics

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Introduction: Activating mutation of the calcium-sensing receptor gene (CASR) reduces parathyroid hormone secretion and renal tubular reabsorption of calcium, defined as autosomal dominant hypocalcemia type 1 (ADH1). Patients with ADH1 may present with hypocalcemia-induced seizures. Calcitriol and calcium supplementation in symptomatic patients may exacerbate hypercalciuria, leading to nephrocalcinosis, nephrolithiasis and compromised renal function.

Presentation: We report on a family with seven members over three generations with ADH1 due to a novel heterozygous mutation in exon 4 of CASR: c.416TC. This mutation leads to substitution of isoleucine with threonine at the cysteine-rich domain of the extracellular domain of CASR. The mutation cosegregated with hypocalcemia in all seven individuals, whereas four unaffected normocalcemic members of the family did not exhibit the mutation. Modeling of the wild-type Ile139 and mutant Thr139 residues (high-resolution cryo-EM and Pymol) showed that the side chain changing from large aliphatic residue to a small neutral one was predicted to form an additional hydrogen bond between residue Thr139 and Ile33. HEK293T cells transfected with wild type or mutant cDNAs demonstrated that p.Ile139Thr substitution led to increased sensitivity of the CASR to activation by extracellular calcium relative to the wild type CASR (EC50 of 0.88 ± 0.02 mM vs.1.1 ± 0.23 mM respectively, p0.005). Confocal images showed that wild type and p.Ile139Thr CASRs were similarly expressed at the periphery of the HEK293T cells, consistent with cell surface localization of the p.Ile139Thr CASR.

Clinical characteristics of ADHA1 patients included seizures (two patients), nephrocalcinosis and nephrolithiasis (three patients), and early lens opacity (two patients). In three of the patients, serum calcium and urinary calcium-to-creatinine (Ca/Cr) ratio levels obtained simultaneously over 49 patient-years (n = 42 paired measurements) were highly correlated (R = 0.623, p 0.001). To calculate the highest serum calcium level associated with calcium excretion in the upper normal range, we plugged age-adjusted upper levels of urinary Ca/Cr ratios into the correlation equation. Since urinary Ca/Cr ratio significantly decreases especially over the first years of life, we came up with age-adjusted serum calcium levels that are high enough to reduce hypocalcemia-induced seizures and low enough to prevent hypercalciuria.

Conclusion: We report on a novel CASR mutation in a three-generation kindred. Comprehensive clinical data enabled us to suggest an optimal age-specific upper limit of serum calcium levels, considering the association between serum calcium and renal calcium excretion.

Engaging the Endocannabinoid System to Overcome Drug Resistance in Neuroendocrine Neoplasms (NENs)

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Background: Patients with unresectable advanced NENs receive systemic treatments with limited non-curable efficacy due to drug resistance. Current literature suggests a palliation effect only for the endocannabinoid system (ECS), despite increasing evidence on ECS possible anti-cancer traits via delaying drug resistance-related pathways. Still, little is known on the ECS crosstalk with NENs drug resistance.

Aims: To understand the possible anti-tumor role of the ECS in NENs and its potential use to overcome resistance to conventional NEN therapy.

Materials and methods: The endocannabinoid receptors (ECR) expression on multiple NENs cell lines and human tumor samples was profiled using FACS/immunofluorescence staining and RNA-Seq. Following either ECR activation or inhibition, NENs cell viability and apoptosis were evaluated by using WST-1 and Annexin/PI staining. Cell cycle was examined with PI staining or CFSE labelling. In vivo anti-tumor effect was tested in NENs mice model following treatment with Everolimus, ECR-antagonists and their combination. Moreover, an innovative NENs reporter xenograft model was developed to monitor tumor growth rate in a high-resolution dimension.

Results: ECR expression on NENs cell lines and primary NENs samples is altered compared with normal cells. Activation of ECS showed diverse effects, with unique cannabis compounds that induced extensive cell death via cell cycle arrest. NENs cell viability was gravely impaired following ECR blocking, whereas exposure of NENs cells to unique cannabis compounds rescued cells from death. The combination of Everolimus with unique cannabis compounds or ECR antagonists increased NENs cells death and prevented drug resistance. Noteworthy, the combination of everolimus with ECR antagonists synergistically and significantly reduced tumor size in NENs mice model. Calibration of a novel reporter xenograft model showed that the regular tumor evaluation method underestimates tumor biomass, allowing an accurate tumor quantification and expansion pattern evaluation.

Conclusion: ECS blocking, alone or combined with standard therapy, significantly inhibits NENs cell proliferation and tumor growth, both in-vitro and in-vivo, overcoming drug resistance. The development of a novel reporter xenograft model allows a dynamic and accurate tumor biomass measurement.

Efficiency of Somatostatin Analogues (SSA) as adjuvant treatment to prevent recurrence of neuroendocrine tumours (NETs) post-surgery.

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Introduction: SSA are a common treatment for patients with NETs. For some patients SSA are shortly used as bridge before surgery while for others SSA represent a chronic treatment option as shown in PROMID and CLARINET studies. There is no clear data on the adjuvant SSA use post operation in patients with high risk of persistent microscopic disease.

Aims: To assess if adjuvant SSA therapy delays recurrence of NET in high-risk patients compared to follow up only, and what are the adverse effects of adjuvant treatment.

Materials and methods: A retrospective study of 43 consecutive patients with G1 to G3 well differentiated NET, who undergone curative surgery and have at least 5 years of follow up. Patient data including demographics, tumor type, imaging, surgery & pathology reports, treatment regime and follow up were collected. Statistical analysis was performed (Mann-Whitney test, chi-square ($\chi 2$) test or Fisher`s exact test, Kaplan-Meier model with a log-rank test, and COX regression model). All statistical tests were two tailed, and a p-value of ≤ 0.05 was considered statistically significant. Disease recurrence was the primary outcome, while adverse effects of SSA were secondary outcomes.

Results: The study group included 24 patients that received SSA treatment, and the control group included 19 patients who had follow up only. We've collected a heterogenous group of NETs including GI-NET, Lung-NET and Pancreatic NET. The Study group was treated with either lanetrotide Autogel or octreotide LAR once every 4 weeks. The control group was followed only. Preliminary results showed no statistically significant difference in outcomes with the study group reaching a mean of 116.951 months (±6.695) and the control group reaching 120.973 months (±14.900), p-value=0.597. By using a multivariate COX regression we've seen that Ki67 is a significant parameter on the recurrence of disease (adjusted HR=1.265; 1.083-1.479), while the adjusted OR of SSA therapy is 7.869 (0.655-94.534) but without statistical significance sig.= 0.104. Lympho-vascular involvement, lymph nodes metastases and perineural invasion had no significance on disease recurrence. We've also found that the most common side effect reported was diarrhea (p-value=0.02).

Conclusion: These preliminary results suggest that the Ki67 of the resected tumor represents a significant parameter for disease recurrence and implying its consideration in SSA adjuvant treatment decision versus follow-up only. Further data emerging from a larger number of patients is pending.

E-Poster Exhibition

These abstracts are presented only in the E-posters exhibition.
for posters that are presented also in "Poster presentation" in oral sessions please see above

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Sexual Behavior and Hormone Gene Expression in the Labyrinthici Fish Blue Gourami (*Trichogaster trichopterus*)

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The blue gourami (*Trichogaster trichopterus*) that has a Labyrinth organ which relatively little information has been published, is a model for hormonal control of reproduction in Anabantidae fish. The genes expiration of hormones involved in reproduction of males and females blue gourami are: Kisspeptin 2 (Kiss 2) and its receptors 1 and 2 (KissR 1 and 2); gonadotropin-releasing hormone 1, 2 and 3 (GnRH1, 2 and 3); GnRH receptor; pituitary adenylate cyclase-activating polypeptide (PACAP) and its related peptide (PRP); somatolactin (SL); follicle-stimulating hormone (FSH); luteinizing hormone (LH); growth hormone (GH); prolactin (PRL). The FSH and LH act on the ovary to synthesize steroids, 17β-estradiol (E2); testosterone (T); vitellogenesis (VTL); and 17α,20β- dihydroxy-4-pregnen-3-one (17,20P). A proposed quality model is presented regarding the brain control oogenesis and spermatogenesis in blue gouram.

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Non Interventional Weight Changes Are Associated With Alterations In Uric Acid Levels

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Background and aims

Uric acid (UA) is an emerging cardiovascular risk factor. Obesity is associated with higher UA levels. We aimed to assess whether non interventional modest weight changes affect UA levels.

Methods

This is a retrospective analysis of subjects referred to annual medical screening. Body mass index (BMI) and UA were measured annually. Patients were divided according to the change in BMI between visits: reduction of 5% ("large reduction"), reduction of 2.5-5% ("moderate reduction"), reduction of 2.5% or elevation of 2.5% ("unchanged"), elevation of 2.5-5% ("moderate increase") and elevation of 5% ("large increase"). The primary outcome was the change in UA between visits.

Results

The final analysis included 19183 subjects. Mean change in UA (mg/dL) was -0.21, -0.04, +0.04, +0.12 and +0.19, for “large reduction”, “moderate reduction”, “unchanged”, “moderate increase” and “large increase”, respectively (p .01). The proportion of patients with 10% rise in UA progressively increased with the relative change in BMI (17.1%, 20.6%, 23.3%, 27.2%, and 33.1% for "large reduction”, “moderate reduction”, “unchanged”, “moderate increase”, and “large increase”, respectively, p .01). Compared to the “unchanged” group, the odds ratio for UA rise of 10% was 0.68, 0.85, 1.22 and 1.61 for "large reduction”, “moderate reduction”, “moderate increase”, and “large increase” groups, respectively (p .01).

Conclusions

Even modest non-interventional weight changes are associated with alterations in UA levels.

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Weekly Vs. Monthly Bisphosphanates Compliance And Adherence A Prospective Cohort Study

Nirit Aviran

Bisphosphanates (BP) are first line treatment for preventing Osteoporotic fractures which cause increased mortality and morbidity . It is well known that there is a very low adherence rate to (BP) therapy for many reasons .
Previous studies have shown a 60% drug discontinuation rate of 2 years following commencement of treatment .
In this big data study, we examine BP adherence and compliance in a large digital registry of patients medically insured by Maccabi Healthcare Services
This cohort includes 150 000 patients with OP according to BMD or who previously had an osteoporotic fracture or/and were receiving drug therapy for Osteoporosis .
The OP registry includes men and women above the age of 50 years , and the data was collected between the years 2010 -2019 ,

We defined good adherence to BP therapy as above an 80% drug purchase rate .
Bias conditions include switching drugs or a temporary drug holiday due to tooth extraction .
Bias can be also because the sample is very large.
Statistical analysis was done using the the SPSS Program .
A p value less than 0.05 is statistically significant .

Results:
Oncologic patients and patients with a low socioeconomic status preferred a monthly regimen , whereas patients with Peptic Disease preferred a weekly regimen .
A possible explanation could be Less drug burden for the first group probably because they need to take many pills anyway, the lower price of monthly Risedronate (Ribone) vs. weekly Alendronate (especially Fosavance) for the second group, and less Gastrointestinal side effects for the last group .
It is interesting to note that the Diabetic and Hypertensive patients preferred a weekly regimen .

Our study suggests consideration of recommending monthly over weekly BP therapy , especially according to the preference of certain groups of patients discussed above , as well as considering recommending intravenous Zoledronic acid which is prescribed annually or even less frequently , in order to improve patient compliance .

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THE ROLE OF VITAMIN D IN THE TREATMENT OF COVID-19 DISESE- MODE OF ACTION

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THE ROLE OF VITAMIN D IN THE TREATMENT OF COVID-19 DISESE - MODE OF ACTION

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Introduction: Recent studies suggest an inverse link, between serum vitamin D levels and disease severity, and mortality rate in Covid-19 patients. Such patients are suffering from unregulated inflammation storm caused by the excess production of cytokines by the immune system. Some clinical studies support the beneficial effect of vitamin D supplementation in the treatment of covid-19 patients.

Aims: The purpose of the present study was to provides evidence for the anti-inflammatory activity of the active metabolite of vitamin D, namely,1,25-Dihdroxyvitamin D, and to shed a light on its mode of action.

Methods: Human peritoneal Macrophages were obtained from effluent dialysates of chronic kidney disease patients. Isolated Macrophages were incubated with vitamin D preparations, followed by LPS incubation. Protein levels of Tumor Necrosis Factora (TNFa) were determined by ELISA, and TNFa - 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, IkBa and of its phosphorylated form were evaluated.

Results: It was found that 1,25-Dihdroxyvitamin D, and its synthetic analog 1,24(OH)2D2, downregulate the expression of TNFα in human macrophages, as well as in a murine macrophage cell line. The results elucidate the mode of action by which 1,25(OH)2D3 inhibits the migration of NFkB from the cell cytosol to the nucleus. NFkB is the main transcriptional factor for TNFα. Thus, inhibition of its migration to the cell nucleus reduces TNFα synthesis, and reduces the inflammatory storm developed in Covid-19 patients.

Conclusions: These findings provide the biological base and the possible 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 the treatment of Covid-19 disease.

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Outpatient obesity clinic –a small solution to a big problem

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Background

Obesity is a global pandemic with increased morbidity and mortality. Rates of obesity in Israel are one of the highest among OECD countries with higher prevalence in the north and south regions. Outpatient obesity clinics have gained popularity with the objective of losing weight. There is a lack of data on treatment outcome in those clinics.

Aim

To report the impact of obesity outpatient clinic on weight loss

Methods

Since May 2020 an outpatient obesity clinic has been functioning in our institution. It consists of an endocrinologist that interviews the patients and recommends changes in life-style (LS) and possibly pharmacotherapy or bariatric surgery. This retrospective study included patients visiting the clinic between 5/2020 and 12/2022 with the objective of losing weight and with at least one follow-up visit. Treatment modalities as well as demographic, clinical and biochemical data were reviewed.

Results

70 patients fulfilled inclusion criteria. Mean age was 48.9 years, 72% were female. 12% Bedouin. 46 patients were bariatric surgery naïve and 24 had a history of bariatric surgery. Mean and median BMI at baseline were 36.8 and 35.95 respectively. Treatment groups included LS recommendations only, LS+ Liraglutide and LS + semaglutide. Mean weight reduction in bariatric surgery naïve patients was 1.15kg, 1.68kg and 6.58kg (1%,1.4%.6.5%) in LS, LS+ Liraglutide and LS+ Semaglutide respectively. Weight reduction in patients with bariatric surgery history was 1.74kg, 0.35kg and 5.66kg (1.7%,0.3%,6.3%) in LS, LS+ Liraglutide and LS+ Semaglutide respectively.

Conclusions

In an outpatient obesity clinic based on an endocrine consultation only, treatment with Semaglutide in addition to LS resulted in moderate weight loss while LS and treatment with Liraglutide had no major influence on weight. Weight loss change was not influenced by prior bariatric surgery status.

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Very High Testosterone Levels in a Child- Bearing Woman without Virilization Sings. Not only Laboratory Pitfalls!

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Introduction: High androgen levels and infertility in reproductive women, beyond the most common cause of polycystic ovary syndrome (PCOS), is often a challenge diagnosis. Ovarian steroid cell tumor is considered a rare subtype of hormone-secreting ovarian tumor, accounting for about 0.1% of all ovarian tumors.

Aim: To report a case of extremely high testosterone levels in a woman with secondary amenorrhea but without signs of virilization, and describe diagnostic assessment of testosterone levels.

Methods: Assessing true testosterone levels by three different manufacture methods Centaur (Siemens), Cobas (Roche manufacture), Architect (Abbott manufacture), respectively and extraction procedure with diethyl ether prior to immunoassay.

Case presentation: A 27 years old woman was followed for a presumed ovarian dermoid cyst and PCOS. Two years later hormonal treatment was stopped in intention for conceive, but menstruation did not resume. Evaluation revealed extremely high testosterone level of 22.1nmol/l, (reference value 2.1 nmol/l) measured by Centaur analyzer (Siemens manufacture) without signs of virilization. Levels of SHBG, FSH and LH were within the normal range. The sample was processed by two alternative methods, Cobas (Roche manufacture) and Architect (Abbott manufacture), showing similar results for testosterone: 19.5 and 23.0 nmol/l, respectively. The same values of total testosterone were found after heterophile and nonspecific

antibodies blocking test. At this point, extraction procedure with diethyl ether was performed prior to immunoassay, then testosterone was measured on Cobas/Roche analyzer. A level of 5.6 nmol/l total testosterone was found after the extraction procedure. An abdominal contrast computed tomography scan (CT) confirmed a 30 mm X 36 mm round solid mass in the left ovary, not characteristic of a dermoid cyst. The ovarian mass was resected. Histological diagnosis reveled an ovarian steroid-cell tumor (SCT) not otherwise specified (NOS). Twenty-four hours after the surgery total testosterone level returned to normal range, 0.6 nmol/l. A month after surgery the patient resumed menstruation.

Conclusions: 1. Our case demonstrates that in some instances, the produced testosterone by the tumor can have a selective influence on peripheral tissues causing only menstrual irregularity without virilization. Since these tumors have malignant potential, differential diagnosis of ovarian mass with high levels of testosterone is essential even without signs of virilization. 2. Elimination of the interferences by extraction with diethyl ether demonstrated that the cause of pitfall in total testosterone level was hydro soluble fragments of the steroid hormone pathway which react with testosterone antibodies in the direct assay.

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Viral Infections During Pregnancy Act As The First Trigger For Childhood Type I Diabetes And Other Autoimmune Diseases

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Observations that children and adolescence with Type 1 diabetes (TID) have a different seasonality of month of birth (MOB) than the general population is explained by fetal β-cell damage by viral infections of the mother during pregnancy.

Proof were the finding of anti-Rota antibodies at delivery in mothers and neonates and anti β-cell antibodies in the latter during a Rotavirus epidemic. Reduction in the incidence of TID (age 0-5y) during Rota vaccination serves us proof.

The finding of a different MOB pattern in Thyroiditis, Graves Disease, Multiple Sclerosis and Atopic Dermatitis also points to a viral etiology of these autoimmune diseases. Identification of the specific causal viruses should lead to preventive, possibly combined, vaccinations.

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Sodium glucose transporter inhibitors increase hematocrit and may mask anemia – findings from a real world study

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Aims

Sodium glucose transporter inhibitors (SGLT2i) are an expanding group of drugs for the treatment of diabetes, chronic kidney disease and heart failure. SGLT2i therapy is associated with an increase in hematocrit as a class effect. There is lack of information regarding the clinical magnitude and significance of hematocrit elevation in those patients, especially cardiovascular outcomes in patients with polycythemia and possible masking of lower hemoglobin levels as a sign of potential severe disease.

Materials and Methods

The current study is a retrospective study utilizing electronic data base of a large community healthcare provider. Hematocrit levels and variables with potential effect were compared before and after treatment initiation in adults with type 2 diabetes.

Results

Study population included 9,646 patients who started treatment with Dapagliflozin or Empagliflozin between 01.2015 and 06.2019. Hematocrit levels were significantly higher after treatment initiation (2.03%), with significantly higher elevation among male vs female (2.18% vs 1.78%), 704 new cases of polycythemia and 69 cases of severe polycythemia. Anemia prevalence was significantly lower post treatment (20% vs 31.6%). In multivariable model, gender, smoking status, SGLT2i type, pretreatment hematocrit, diabetes duration, body mass index and glomerular filtration rate change were found to have significant effect on hematocrit change.

conclusions

In this retrospective study SGLT2i was associated with significant hematocrit elevation, new polycythemia cases and lower anemia prevalence. Further studies are needed to determine the clinical significance and approach to patients with pretreatment or on treatment polycythemia and the approach to patients with lower-normal hemoglobin levels under treatment with SGLT2i.

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Severity of hypoglycemic events occurs in outpatient settings related to recommendations given at discharge.

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Background

Hypoglycemia is associated with an increased risk of emergency room visits, increased rate of hospitalizations, and impaired quality of life. Recommendations given to patients with DM at discharge could improve diabetes control in outpatient settings albeit could be related to hypoglycemic events in outpatient settings.

Aim of the study

To check the relation of hypoglycemic episodes and their severity with the recommendations given at discharge

Results

The study found a significant correlation between hypoglycemic events in outpatient settings with the recommendations to change diabetes treatment at discharge (p=0.003). The level of blood glucose during the hypoglycemia event was lower in the change treatment group 57.1±9.6 mg/dl vs 59.1 ±8.1 mg/dl no change treatment group (p=0.001).

Conclusion

Hypoglycemic episodes in outpatient settings related to recommendations at discharge. Multiple factors including insulin doses, kidney function, blood glucose control before hospitalization, length of hospitalization, underlying disease, and age of the patients contribute to the frequency and severity of hypoglycemic events.

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PTH Related Hypercalcemia in Pregnancy: Diagnostic Pitfalls and Challenges

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Background PTH-related hypercalcemia during pregnancy is rare and may pose a diagnostic challenge.

Clinical Case A 37-year-old 12 weeks gravida 1 asymptomatic woman was hospitalized for albumin-corrected serum calcium of 12.3 mg/dl. Serum phosphor, PTH, and vitamin D were 2.3 mg/dl, 73 pg/ml (6.7-38.8), and 25 ng/ml respectively.

Her past medical history is notable for primary hyperparathyroidism (PHPT) diagnosed at the age of 17. She underwent left neck exploration but remained hypercalcemic. The pathology of a 3 mm lesion excised from the caudal aspect of the left thyroid lobe was interpreted as a normal parathyroid gland, and a 5 mm hypercellular parathyroid lesion was found in the thymic tissue. The family history was negative for hypercalcemia and nephrolithiasis. The preconception calcium-creatinine clearance ratio (CCCR) was 0.024 and reached 0.034 during pregnancy.

Serum calcium levels declined to 11 mg/dl upon hydration allowing for patient discharge, but she was re-admitted after two days as calcium rapidly rose back to 12.3 mg/dl. Since hypercalcemia, and in particular high levels as those found in this patient may be associated with increased maternal and fetal morbidity, urgent definitive diagnosis and treatment were warranted. An inconclusive 3X5 mm hypoechoic nodule was visualized below the inferior pole of the right thyroid lobe by US, and a T2-based neck and upper mediastinum MRI demonstrated two right hyper-intense nodules consistent with enlarged parathyroid glands.

The patients` young age at diagnosis and the apparent multi-glandular disease suggested a possible diagnosis of syndromic or familial PHPT. The pre-conception CCCR did not support the diagnosis of familial hypocalciuric hypercalcemia, but the rare familial hypercalcemia and hypercalciuria syndrome caused by mutations in the cytoplasmic tail of the calcium-sensing receptor could not be excluded. The absorptive hypercalciuria of pregnancy precludes the use of CCCR as a diagnostic tool.

Serum and urine calcium levels of family members were unremarkable. The patient underwent urgent genetic testing to avoid unwarranted parathyroid surgery or alternatively to assist in the operative planning. Sequencing analysis of AP2S1 CASR CDC37 CDKN1A CDKN1B CDNKN2B CDKN2C TRPV6 GNA11 MEN1 RET and GCM2 genes was negative for mutations.

The surgeons successfully identified and resected an enlarged 15 mm right parathyroid adenoma and preserved a normal-looking parathyroid gland. Intra-operative PTH dropped by 90% and post-operative serum calcium normalized.

In conclusion, clinical characteristics of sporadic and familial PHPT may overlap considerably, necessitating a multidisciplinary team approach, particularly during pregnancy.

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Temporal characteristics of patients admitted to internal medicine department with Heart Failure

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Background: Heart failure (HF) is a global problem with significant morbidity and mortality. Diabetes is known to increase the risk of HF, and a substantial proportion of hospitalized patients with HF has diabetes. Data are inconsistent on the prognostic significance of acute decompensated HF (ADHF) with and without diabetes.

Objectives: To characterize hospitalized ADHF patients with and without diabetes and to identify their clinical outcome in and after indexed hospitalization.

Methods: This was a single center retrospective cohort study. All consecutive hospitalized patients with a principal diagnosis of ADHF between 1/1/2010 to 31/12/2019 were included. Patients were divided into diabetic and non-diabetic. Outcomes included: (1) length of hospitalization; (2) risk for HF and all-cause re-hospitalization after one year; (3) mortality rates in hospitalization and one year post discharge; (4) the influence of glycemic control in the diabetic population on the above targets.

Results: The final analysis included 787 patients with ADHF, of which 62% had a previous diagnosis of type 2 diabetes mellitus (T2DM). Exacerbating factors included mostly infections (32%) and noncompliance to HF medications (23%). Patients with diabetes had significantly higher rates of comorbidities such as hyperlipidemia, obesity, ischemic heart disease (IHD), previous myocardial infarct (MI) and peripheral vascular disease (PVD). However, no significant differences occurred in any of the clinical outcome parameters: length of hospitalization (6±5 vs 6±4, p=0.377), risk for re-hospitalization (51% vs 56%, p=0.154), mortality in hospitalization (10% vs 10%, p=0.675) and mortality one year after hospitalization (22% vs 25%, p=0.389) in diabetes compared non diabetes patients. The clinical outcomes of patients with diabetes were independent of glycemic control.

Conclusions: T2DM is common among patients admitted with ADHF. In our study clinical outcomes of patients hospitalized with ADHF were not affected by additional T2DM. These findings indicate that primary prevention interventions are greatly needed, as well as implementing guidelines for diabetes and HF management to improve outcomes in the following years.

DIFFERENCES IN HOSPITALIZATION OUTCOMES OF DIABETIC KETOACIDOSIS IN PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS

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Background

Diabetic ketoacidosis (DKA) is a hazardous medical emergency complicating diabetes, most often in patients with type 1 diabetes (T1DM) but also in type 2 (T2DM). The introduction of sodium-glucose co-transporter (SGLT2) inhibitors has increased attention to DKA among patients with T2DM. We aimed to study and compare clinical characteristics and outcomes of DKA in hospitalized patients according to diabetes type.

Methods

We conducted a retrospective cohort analysis of outcomes among 204 patients admitted with DKA to Shamir medical center (2013-2021). Patients were identified by ICD-9 code for DKA and the diagnosis was confirmed using strict criteria according to the American Diabetic Association. Patients were divided by DM type, which was verified by treatment history, autoantibody status and/or an endocrinologist's ambulatory visit record. Subject's characteristics, laboratory data, and hospitalization outcomes were retrieved by a chart review, and a comparison between patients with T1DM and T2DM was executed. Outcomes of T2DM patients with and without SGLT-2 treatment were also evaluated.

Results

The study cohort included 126 patients with T1DM, and 78 with T2DM. The latter group was significantly older (62.9 vs. 35.2 p0.001), with an advanced complex of comorbidities, and micro- and macrovascular complications. Patients with T1DM had a significantly shorter time to DKA resolution (p=0.027) and a shorter length of hospitalization (p 0.001). Mortality occurred only in patients with T2DM - 6.4% vs 0% p

Conclusions

Patients with T2DM hospitalized with DKA have adverse hospitalization outcomes that can partly be attributed to their older age and complex comorbidities. SGLT2 treatment did not have an additional adverse effect on outcomes.

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Freestyle Libre 2 as Adjunct to Glucose monitoring in Gestational Diabetes Mellitus (GDM)

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Background: Kuppat Cholim Meuhedet was the first HMO in Israel to initiate use of Freestyle Libre 2 (flash glucose monitoring system with alarms for both high and low blood glucose) for use in GDM diagnosed at week 24 to 28. Women diagnosed with GDM are instructed to measure their blood glucose fasting, one hr after each meal and before going to bed; at least five times daily. For many women monitoring their blood glucoses are very tedious. The diabetes clinic staff often has to contend with getting less than adequate information to help in the decision to treat the patient with insulin or metformin and for dose titration. Recent data suggest that even more stringent targets and greater attention to overnight glucose profiles may be required to normalize outcomes in GDM.

Aim: Establish if libre glucose values can replace glucometer values

Methods: Patients diagnosed with GDM during week 24-28 of their pregnancy were giving a glucometer and a libre for the duration of the pregnancy. They were requested to obtain fasting glucose values both on glucometer and libre. In addition to scan the libre before and hour after eating and before going to bed. Women were asked to obtain glucometer value at least once after a meal or when the libre value was above a 130mg%.

Patients were asked as to the benefits of the libre and if they chose to use it for the rest of the pregnancy or the next pregnancy.

Results: 93 fasting glucose values were obtained by libre and glucometer each. The fasting glucose values obtained with the libre were significantly different than those achieved on glucometer (98 vs. 92mg%; p0.01). 76 values were obtained one hour after a meal with both libre and glucometer. Although the difference was not statistically significant (124 vs 117mg%; 0.07), further studies will need to determine if of clinical significance.

All women wanted to continue with the libre because of the convenience and less finger sticks. They all mentioned the assurance obtained with libre and being able to see how different foods affect their blood glucose.

Conclusion: These findings suggest the need for further research in order to decide whether clinical decisions can be made with libre and whether if so, fasting glucoses should have a different cut-off value. In addition, it remains to be seen if Time In Range obtained by this method is useful in GDM.

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Does The “Obesity Paradox” Have An Expiration Date? A Bigdata Retrospective Cohort.

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Background: Although obesity and overweight are associated with increased morbidity and mortality, higher body mass index (BMI) has been shown to be a protective factor from mortality in patients with acute infectious disease, also known as the “obesity paradox”. Yet, whether these effects persist at long-term follow-up is unknown.

Objective: To investigate the relationship between BMI and mortality after hospitalization with an infectious disease in a five-year follow-up period.

Methods: A retrospective analysis of 25,226 adult patients admitted with an acute infectious disease between 2010-2020 to Shamir Medical Center, Israel, was conducted. We compared patients in different BMI categories: underweight 15-18.5 kg/m², normal-weight 18.5-25 kg/m², overweight 25-30 kg/m², obesity class-I 30-35 kg/m², obesity class-II 35-40 kg/m², and obesity class-III 40-45 kg/m², regarding mortality during hospitalization and follow-up.

Results: Patients in the different BMI categories were heterogeneous regarding baseline demographics and comorbidities, as well as infectious syndrome at index hospitalization. In-hospital mortality and one-year mortality were higher in underweight and normal-weight patients as compared to all other categories, 22% and 13.2% vs 7-9% (p0.001) in-hospital, and 31.8% and 20.6% vs 13-15.6% (p0.001) at one year. Five-year mortality was only significantly higher in the underweight group 44.4% vs 30.8%-36.1% (p0.001). In multivariable logistic regression models, adjusted for age, sex, comorbidities, and infectious syndrome underweight was associated with a significantly increased odds-ratio for In-hospital, one-year, and five-year mortality while overweight and obesity were associated with a decreased odds ratio for mortality at all time points. In a survival analysis model, all classes of obesity were associated with a decreased risk of mortality compared to normal weight while underweight was associated with increased risk (five-year mortality HR 2.02, p0.001)

Conclusions: Among patients hospitalized with infectious disease, underweight and normal-weight BMI were associated with an increased risk for mortality up to one year after discharge.

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Impact of Bariatric Surgeries in Females on Their Offspring Growth and Development

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Bariatric surgery has become increasingly common among young women of reproductive age. Approximately half of the bariatric surgeries performed each year in Israel are carried out on individuals under the age of 40, with the majority being performed on women. It was reported that bariatric surgery is associated with a higher risk for small for gestational age (SGA) births. The purpose of this study is to explore the impact of maternal bariatric surgery on the growth and development of children with respect to surgery type, time between surgery and birth, sex of the child and other medical parameters. We collected data of 6,500 mothers who underwent bariatric surgery in Jerusalem hospitals and their offspring up to the age of six. The data was obtained from the Israeli Ministry of Health, Hadassah Medical Center and Shaarei Zedek Medical Center. A comparison group of 200,000 births of other newborns and those born by the same mothers prior to the surgery is also included in the analysis. Preliminary analysis confirmed a higher occurrence of SGA births, and a rapid growth in the first year on the newborn life. The findings of this study will contribute to our understanding of the impact of bariatric surgery on maternal-fetal health and inform healthcare policies and practices.

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Predictors of Endocrine Recovery and Deficits Following Transsphenoidal Surgery for Sellar Masses

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OBJECTIVE: There are limited data on the impact of transsphenoidal surgery (TSS) for pituitary masses on hormonal function. The objective of this study was to determine the risk for new-onset hypopituitarism or resolution of preoperative endocrine deficits following TSS.

METHODS: A retrospective analysis of patients who underwent TSS at Beilinson Campus, Rabin Medical Center, between 2010 and 2020. Demographic, clinical, laboratory and radiological data were retrieved from electronic medical charts, including data on cortisol, thyroid and sex-hormone deficiencies.

RESULTS: The cohort consisted of 101 patients (56% male; mean age, 48 years) including 42 (41.6%) non-functioning pituitary adenoma, 22 (21.8%) growth hormone-secreting adenoma, 18 (17.8%) ACTH-secreting adenoma, 13 (12.9%) prolactinoma, 2 (2%) TSH-secreting adenoma, and 4 (4%) other masses.

On presentation, 53 patients (52.5%) had no hormonal deficit, while 39 (38.6%) had central hypogonadism, 18 (17.8%) were diagnosed with central hypothyroidism, and 12 (11.9%) had central hypocortisolism. In most cases (31.7%) there was only one hormonal deficit, 11 patients (10.9%) had deficiencies of two axes and 5 (5%) had a defect in all three axes.

Fifty-five patients had preoperative normal gonadal function, 8 (14%) of which developed new-onset hypogonadism following TSS. Thirty-nine patients (36 male, 92.3%) had preoperative central hypogonadism, 16 (41%, all male) of which had their reproductive axis recovered.

Seventy-six patients had preoperative normal thyroid function, 12 (16%) of whom developed new hypothyroidism. Eighteen patients (14 male, 78%) had preoperative central hypothyroidism, 8 (44%, all male) of whom had their hypothyroidism resolved.

Eighty-four patients presented with normal cortisol secretion, 9 (10%) of whom developed new post-operative central hypocortisolism. Twelve patients (11 male, 92%) had preoperative central hypocortisolism, 9 (75%) of them had cortisol axis normalization following TSS.

Predictors of new post-operative hypogonadism included pre-operative visual field defect (VFD) (p=0.003), while pre-operative VFD (p=0.04) and an invasive suprasellar mass (p=0.056) predicted new post-operative hypocortisolism. Predictors of hypogonadism recovery included absence of suprasellar extension (p=0.068) or VFD (p=0.03) and younger age (p=0.002), while male gender predicted greater likelihood of hypothyroidism recovery (p=0.07).

CONCLUSIONS: Our data suggest that resolution of at least one hormonal deficiency may occur in 4 of 10 patients undergoing TSS for a sellar mass. Interestingly, the cortisol axis was most likely to improve in our cohort. New postoperative hormonal deficiency may occur in 10-16% of patients. More data are needed to better predict resolution or development of endocrine deficits following TSS.

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Thyroid hormone levels predict long-term Survival

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Background: Lower levels of free tri-iodothyronine occur during acute illness, as part of "euthyroid sick syndrome" (ETS), a chronic form of this syndrome also exists.

Objective: To determine whether thyroid hormone levels can predict long-term survival.

Design & Setting: This is a "big-data" study of thyroid function tests from samples taken between 2008-2014. Data were crossed with electronic records for morbidity and mortality.

Measurements: Test results were converted to Age and Gender Adjusted Percentile (AGAP). The hazard ratio for death was crossed with ranges of initial AGAPs for two subgroups: "not healthy" - subjects with at least one of five chronic conditions registered in their electronic health chart; "healthy" – all others.

Results: Samples from 258,695 individual remained after exclusion criteria: 151,868 "not healthy" and 106,827 "healthy". After a median of 6.8 years, 5,865 /151,868 (10.4%) of the "not healthy" had died and 2,504/106,827 (2.3%) of "healthy" participants. Low initial FT3 AGAPs were predictive of poor survival. The Hazard Ratio (HR) for survival was compared between the lowest 5th percentile and highest 95th percentiles for initial FT3 AGAPs. The HR for "not healthy" participants was 5.71 (CI – 5.23 to 6.26, p0.001), and for "healthy" - 3.92 (CI – 3.06 to 5.02, p0.001)). Greater than 50% decline in FT3 AGAPs was associated with a decline in survival. For 34,129 patients with such decline, eight year survival declined by 3.75% for "not healthy" subjects and 2.0% for "healthy" subjects.

Conclusion: Low FT3 AGAPs, representing ETS, predicted poor survival, more strongly among "not healthy" people.

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New concepts to tackle non-adherence to medical recommendations in chronic diseases: analysis and comparison between six design outcomes of collaborative work between designers and diabetes specialists

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Background
Adherence to medical recommendations is still low in chronic diseases such as diabetes. This gap has a personal, societal, and economic burden. Collaborative work using design thinking methodology led to six different concepts to improve adherence (tool for intimidation conversation DIATALK, guess result application DIAGUESS, playing application DIAPLAY, automatization of psycho-social support DIASUPP, vacation for therapeutic patient education DIACATION, family integration in the health care system DIAFAM)
Methods
Evaluation of these six concepts was done through an anonymous questionnaire. Every participant was asked to grade on an agreement scale from 1 (totally agree) to 5 (totally disagree) clearness, usefulness, patient-friendly, health care professional (HCP)-friendly, feasibility in the health system as well as an overall ranking of the six concepts. Profession, age, experience in the working place, position, diabetes (people with diabetes PWD), and diabetes in family were recorded for analysis through Cronbach`s alpha and pair comparison through Fisher's LSD test.
Results
Seventy-nine participants answered the questionnaire,74 of them with complete answers (14 designers, 48 HCP,12 others) of whom 18 had diabetes and 46 a family history of diabetes. DIACATION (0.019) and DIAFAM (0.0747) were significantly clearer concepts than DIATALK according to all responders. The DIATALK was ranked the lowest according to all responders (1.030456e-10 Friedman test) with no significant difference between other concepts and was perceived more HCP friendly by PWD or by others compared to HCP and the less patient friendly by PWD or diabetes in family. Answers did not differ according to age or experience in the working place. Respondents with position Manager/Self found DIAGUESS more feasible in the long term than respondents with other positions. People with diabetes in family found DIAFAM less feasible than people with no diabetes in family. No difference was found for ranking according to diabetes, diabetes in family, profession. DIAGUESS and DIAFAM had the highest score for concomitant ranking and feasibility compared to the other concepts.
Conclusion
Collaborative work of designers and HCP can bring innovation to tackle the gap in adherence to medical recommendations. Careful analysis of all stakeholders is mandatory to develop new ways to increase adherence to medical recommendations.

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Romosozumab versus Zoledronic acid in Women with Spinal Cord Injury and Low Bone Mineral Density

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Objective:

Spinal cord injury (SCI) triggers immobilization and unloading resulting in dramatic bone loss and fractures. There is paucity of data regarding bone-protective treatment in patients with chronic SCI. Targeting immobilization-induced sclerostin pathway showed promise in animal models of SCI. We aimed to investigate the effect of Romosozumab vs. Zoledronic Acid (ZA) in women with SCI.

Materials and methods:

Women with SCI of at least 24-month duration and a T-score of -2 or less at either lumbar spine, femoral neck or total hip, were randomized to an open-label SC Romosozumab 210 mg/monthly for one year vs. single-dose IV ZA 5 mg. The primary outcome was total hip (TH) BMD change at 12 months. Secondary end points were femoral neck BMD and bone turnover markers.

Results:

Five women with Grade A (motor and sensory complete) according to American Spinal Injury Association (ASIA) impairment scale were randomized and completed one year of follow-up. One patient in the Romosozumab group was excluded from analysis due to sacral osteomyelitis secondary to preexisting pressure sore and significant catabolic state. At baseline, TH BMD T-score ranged between -2.4 and -5.7. Results are presented in a Table. Two participants received Romosozumab and two, ZA. Following 3 month of Romosozumab treatment, N-terminal propeptide of type 1 collagen (P1NP) increased by 1.6% and 44%, yet both subjects exhibited an increment in TH BMD of 6.6% and 9.8%, at 12 months, respectively. In ZA-treated subjects a 5.2% and 10.3% increase in TH BMD was demonstrated as well. Medication-related adverse events were limited to injection site reactions in Romosozumab and flu-like symptoms in ZA-treated subjects.

Conclusion:

In this small study, both monthly Romosozumab and single dose ZA seem to induce a BMD gain in women with chronic SCI. Larger studies targeting bone loss in this unique group of patients are warranted.

Disclosure:

The study was investigator-initiated and supported by Amgen.

Table:

Patient, treatment	Age, years	Time from SCI, years	Baseline TH BMD, g/cm^2	Baseline TH BMD, T-score	TH BMD increment at 12 months, g/cm^2	TH BMD increment at 12 months, %
1, Romosozumab	30	7	0.701	-2.5	0.069	9.8
2, Romosozumab	26	3	0.531	-3.8	0.035	6.6
3, ZA	44	4	0.710	-2.4	0.037	5.2
4, ZA	55	11	0.289	-5.7	0.030	10.3

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Maternal Dysglycemia and offspring weight: Is iodine intake a modifier?

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Background:

Maternal hyperglycemia, even below the diagnostic threshold for diabetes, is associated with increased birth weight. Several studies suggest a link between maternal iodine deficiency (ID) and increased newborn weight. Still, it is unclear how maternal glycemic and iodine status influence birth weight in mild-to-moderate ID.

Aim:

To examine the relationship between birth weight and between maternal blood glucose and iodine intake levels in pregnant women with mild-to-moderate ID.

Methods:

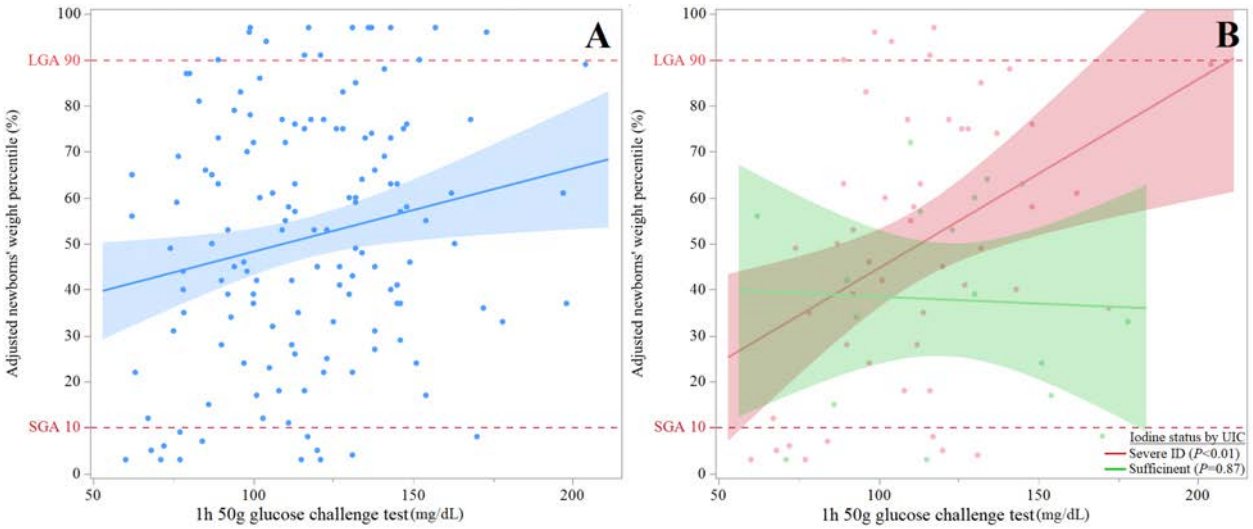
The study evaluated pregnant women`s glucose levels and iodine status using 1h 50g glucose challenge test (GCT), non-fasting glucose before delivery, an iodine food frequency questionnaire, serum thyroglobulin (Tg), and urinary iodine concentrations (UIC). Thyroid function tests and autoantibodies were sampled at recruitment. Anthropometric and obstetric data were collected at recruitment and delivery. A Cox proportional hazards model with multiple confounders was used to predict large for gestational age (LGA).

Results:

There was a significant correlation between GCT values and adjusted newborn weight percentiles (Figure A). Participants with UIC values indicating presumably severe ID also showed this significant positive correlation, but not those with UIC values indicating sufficient iodine (Figure B). For the Cox model, 15 variables with a known or probable association with neonatal weight were used. A Tg 13 μg/L, suggestive of iodine insufficiency, was independently associated with LGA (adjusted hazard ratio = 3.4, 95% CI: 1.4–10.2, p = 0.001). Maternal Tg17μg/L values were five times more likely to result in LGA newborn (OR = 5 [95% CI 1, 18]; p 0.01). Estimated iodine intake correlated with FT4 among participants reporting iodine-containing supplements (ICS) after confounders` adjustment (β = 0.4 95 %CI: 0.0002-0.0008, p=0.001). Moreover, adjusted maternal FT4 values inversely correlated with newborn weight percentiles (β=-0.2 95 %CI:-0.08 - -56.49, p=0.049).

Conclusion:

Maternal insufficient iodine status may increase LGA risk in mild-to-moderate ID regions. Sufficient iodine status and ICS consumption may restrain and modify the effect of maternal hyperglycemia on offspring`s weight. Further investigation should focus on the relationship between maternal ID and newborn`s weight via maternal T4, among pregnant women with Dysglycemia.


A
B
LGA 90
SGA 10
Adjusted newborns' weight percentile (%)
1h 50g glucose challenge test (mg/dL)
Iodine status by UIC
Severe ID (P<0.01)
Sufficient (P=0.87)