האגודה הישראלית לאנדוקרינולוגיה IES Israel Endocrine Society

The 47th Annual Meeting of the Israel Endocrine Society

April 29-30, 2018
Hilton Tel Aviv Hotel

Program & Abstract Book

WELCOME ADDRESS

Dear members, colleagues, and friends,

On behalf of the executive committee of the Israel Endocrine Society, it is our pleasure to welcome you to our 47th annual meeting that will take place at the beautiful, and conveniently located, Tel Aviv beach front Hilton hotel.

We are thrilled to announce that this year, congress attendees will enjoy an unprecedented participation of guest speakers from abroad, as we will host no less than 7 guests, eminent speakers who will come from afar to be with us. We are extremely thankful to them for making the journey. We are no less thankful to our many local invited speakers who didn't travel far but put in the time and effort to contribute to a varied and exciting scientific program.

As in the past, our two day program will hold 4 plenary lectures that will cover a wide range of topics and will be delivered by outstanding speakers: Prof. Raj Thakker, Prof. Raphael Meshulam, Prof. Jeffrey Alan Golden and Prof. Ron Kahn.

There will be altogether 6 parallel symposia that will be geared both at clinicians as well as at basic researchers, and will cover an array of hot and cutting edge topics such as CRISPRCAS9, genome editing, cannabinoids and the metabolic syndrome, and brain and cognition in the metabolic syndrome and diabetes.

As always, we are looking forward to some exciting oral and poster sessions that will showcase the quality endocrine research our members are involved with.

On April 29th, the Israel Endocrine Society will honor Prof. Arie Gertler, one of our society's long term members for his career-long contribution and commitment. Please join us for this informal gathering that will take place in the afternoon, just before the meet-the-professor session.

We are delighted to announce a new prize that will recognize an outstanding clinician whose occupation is for the most part in the community. This prize will become an annual event, very much alike our longstanding Chovers and Lindner awards.

We would like to take this opportunity to express our gratitude to the many volunteers who helped us with suggestions for sessions, with review of abstracts, and with their willingness to chair sessions. We are particularly thankful to Prof. Yoav Sharoni who was responsible for the timely assessment of all abstracts, and their allocation to the various sessions.

We are certain that our joint efforts together with your attendance will make this meeting a remarkable one.

As always, we are thankful to the Paragon company's efficient staff for their professionalism and seriousness. Likewise, we are indebted to our many sponsors. Finally, we would like to thank each and everyone of you for being involved in making our most important event of the year a truly outstanding one.

Looking forward to seeing you soon.

Ruth Shalgi
Chair, Program Committee

On behalf of the IES Executive Committee
Carlos Benbassat, Galia Gat-Yablonski,
Avraham Karasik, Gil Leibovitch,
Rina Meidan, YoelToledano,
Karen Tordjman, Simona Glasberg

IES EXECUTIVE COMMITTEE

תודתנו נתונה לחברות נותנות החסות והמציגים על תמיכתן הנדיבה:

פרופ' הנס יוחנן לינדנר ז"ל – מילים לזכרו

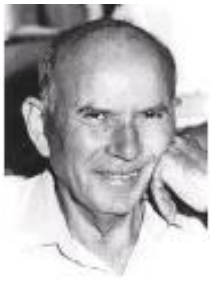
פרופ' הנס יוחנן לינדנר נולד בשנת 1922 בגרמניה ועלה ארצה עם הוריו בשנת 1936. לאחר מלחמת השחרור הוא למד רפואה וטרינארית בסידני (אוסטרליה) וסיים בהצטיינות. את לימודיו לתואר Ph.D. הוא השלים באוניברסיטת קיימבריג' שבאנגליה. עם תום לימודיו, חזר לינדנר לאוסטרליה, התמנה כחוקר בכיר ב- Commonwealth Scientific Research 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 בורנשטיין
2015- איילת ארז
2016- ערן אלינב
2017 – סימונה גלסברג

2018- פרופ' גד אשר

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 שרת 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 לאנדוקרינלוגיה 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 45 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- דר' עמית אקירוב

2018- דר' יוסי תם

SUNDAY, APRIL 29, 2018

07:30-08:30 Registration and Gathering, Exhibition Visit

08:30-10:00 Hormones & Cancer; Other — Hall C

08:30 Efficacy and Safety of Long-acting Pasireotide in Acromegaly: A Multicenter Study

Ilan Shimon[1], Zaina Adnan[2], Alexander Gorshtein[1], Lior Baraf[3], Nariman Saba Khazen[4], Michal Gershinsky[4], Yulia Pauker[4], Ali Abid[2], Mark J Niven[5], Carmela Shechner[6], Yona Greenman[7]
[1]*Endocrinology, Rabin Medical Center, Petah Tikva, and Sackler School of Medicine, Tel-Aviv University*
[2]*Endocrinology, Zvulun Medical Center, Clalit Medical Services, Kiryat Bialik, Israel*
[3]*Endocrinology, Soroka University Medical Center, Beer Sheva, Israel*
[4]*Endocrinology, Linn Medical Center, Clalit Medical Services, Haifa, Israel*
[5]*Endocrinology, Laniado Hospital, Netanya, The Rappaport Faculty of Medicine,The Technion*
[6]*Endocrinology, Bnai-Zion Medical Center, Haifa, Israel*
[7]*Endocrinology, Tel-Aviv Sourasky Medical Center and Sackler School of Medicine, Tel-Aviv University, Israel*

08:42 A Single Parameter or Combination of Parameters for Predicting an Adequate Response to The Short Synacthen Test in Hospital

Lior Tolkin, Michal Vidberg, Gabriel Munter
Department of Internal Medicine and Endocrine Unit, Shaare Zedek Medical Center Affiliated with the Faculty of Medicine, Hebrew University, Jerusalem, Israel

08:54 A New Form of Selective Hypoaldosteronism: Aldosterone Failure to Respond to ACTH is Linked to Glucocorticoid Excess, Normal Cortisol Response to ACTH and Unexplained Malaise

yonit Marcus, Gabi Shefer, Karen Tordjman, Yael Sofer, Yona Greeenman, Etty Osher, Jessica Sack, Maya Ish Shalom, Naomi Even-Zohar, Naftali Stern
Endocrinology, metabolism and hypertension, Tel Aviv Medical Center, Tel Aviv, Israel

09:06 Primary Treatment of Nonfunctioning Pituitary Adenoma with D2 Agonists- A Single Center Experience

Vitaly Medvedovsky[1], Elad Avraham[2], Rosa Novoa[3], Lior Baraf[1], Uri Yoel[1], Dayana Cohen[1], Yuval Sufaro[2], Israel Melamed[2], Merav Fraenkel[1]
[1]*Endocrinology, Soroka University Medical Center, Beer- Sheva, Israel*
[2]*Neurosurgery, Soroka University Medical Center, Beer- Sheva, Israel*
[3]*Radiology, Soroka University Medical Center, Beer- Sheva, Israel*

09:18 Favourable Outcomes of Peptide Receptor Radionuclide Therapy (PRRT) for Treatment of Metastatic Rectal Neuroendocrine Neoplasia (NEN)

Simona Grozinsky-Glasberg[1], Grace Kong[2], Tim Akhurst[2], Michael S. Hofman[2], Amichay Meirovitz[3], Ofra Maimon[3], Arnon Schwartz[4], Michael Michael[5], David J. Gross[1], Rodney J. Hicks[2]
[1]*Neuroendocrine Tumour Unit, Endocrinology and Metabolism Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
[2]*Centre for Cancer Imaging, Neuroendocrine Unit, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia*
[3]*Oncology Department and Radiation Therapy Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
[4]*Nuclear Medicine Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
[5]*Neuroendocrine Unit and Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia*

09:30 Dysglycemia in Non-functioning Pancreatic Neuroendocrine Tumors (PNET): A New Form of Type 3c Diabetes Mellitus?

Esther Osher[1], Ravit Geva[2], Ido Wolf[2], Yona Greenman[1], Karen Tordjman[1], Joseph Klausner[3], Yael Sofer[1], Erez Scapa[4], Ido Nachmany[3], Nir Lubezky[3], Yacov Goihman[3], Guy Lahat[3], Erwin Santo[4], Eliabelle Touati[1], Naftali Stern[1]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[2]*Department of Oncology, Tel Aviv-Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Department of Surgery, Tel Aviv-Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[4]*Department of Gastroenterology, Tel Aviv-Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

09:42 Obesity Among Children and Adolescents With Non Classic Congenital Adrenal Hyperplasia Due to21-Hydroxylase Deficiency

Liat de Vries[1,2], Yael Lebenthal[2,3], Moshe Phillip[1,2], Tenenbaum Ariel[1,2], Rachel Bello[1,2]
[1]*Institute for Endocrinology and Metabolism, Schneider's Children Medical Center in Israel, Petah-Tikva, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[3]*Pediatric Endocrinology and Diabetes Unit, DANA-DWEK Children's Hospital, The Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

08:30-10:00 Diabetes — Hall B

08:30 The RNA Binding Protein PTBP1 is a Key Regulator of Gluconeogenesis

Yaniv Lustig[1,2], Ehud Barhod[1], Rina Hemi[1], Metsada Pasmanik-Chor[3], Hannah Kanety[1]
[1]*Institute of Endocrinology, Sheba Medical Center, Tel Hashomer, Israel*
[2]*Central Virology Laboratory, Ministry of Health, Sheba Medical Center, Tel Hashomer, Israel*
[3]*Bioinformatics Unit, Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel*

08:42 Maturity Onset Diabetes of the Young 2 (MODY2): Insight from an Extended Family

Ghadir Elias-Assad[1,2], Rawnak Saab[3], Jane Molnes[4], Ora Hess[1], Rasmi Abu-Ras[5], Hussein Darawshe[6], Pål Rasmus Njølstad[4], Yardena Tenenbaum-Rakover[1,2]
[1]*Pediatric Endocrine Institute, Ha'Emek Medical Center, Afula, Israel*
[2]*The Rappaport Faculty of Medicine, Technion, Haifa, Israel*
[3]*Baruch Padeh Medical Center, Poriya, Israel*
[4]*KG Jebsen Center for Diabetes Research, University of Bergen, Department of Pediatrics, Haukeland University Hospital, Bergen, Norway*
[5]*Faculty of Medicine, Bar-Ilan University, Zeffat, Israel*
[6]*Family Medicine Department, Clalit Health Service, Gallilee, Israel*

08:54 Involvement of Nitric Oxide and Endothelin Systems in the Pathogenesis of Endothelial Dysfunction in Diabetes

Hiba Yaseen[1,2], Niroz Abu-Saleh[3,4], Hoda Awad[3,4], Mogher Khamaisi[1,2,3], Zaid Abbasi[3,4]
[1]*Internal Medicine D, Rambam Health Care Campus, Haifa, Israel*
[2]*Clinical Research Institute, Rambam Health Care Campus, Haifa, Israel*
[3]*Ruth & Bruce Rappaport Faculty of Medicine, Technion-IIT, Haifa, Israel*
[4]*Department of Laboratory Medicine, Rambam Health Care Campus, Haifa, Israel*

09:06 A Randomized Controlled Trial Comparing a Telemedicine Therapeutic Intervention with Routine Care in Adults with type 1 Diabetes Mellitus Treated by Insulin Pumps

Marianna Yaron[1,2,4], Bruria Sher[2], Daniel Sorek[2], Mina Shomer[2], Noa Levek[2], Tali Schiller[2,4], Monica Gasper[2], Rachel Frumkin Ben-David[2], Kineret Mazor-Aronovitch[2,3,4], Efrat Tish[2], Yoni Shapira[1,2,4], Orit Pinhas-Chamiel[2,3,4]
[1]*Department of Endocrinology, Metabolism and Hypertension,, Tel-Aviv Sourasky Medical Center, Israel, Tel Aviv, Israel*
[2]*National Juvenile Diabetes Center, Maccabi Health Care Services, Raanana, Israel*
[3]*Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical*

Center, Ramat Gan, Israel
[4]*Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel*

09:18 MicroRNA Expression Profile in Human Visceral and Subcutaneous Adipose Tissues during Pregnancy: Implications for Metabolic Adaptations to Normal Gestation and Putative Mechanism in Gestational Diabetes

Mariam Iskilova[1,3], Roni Zemet[2], Rina Hemi[1], Benny Brandt[2], Noam Shomron[3], Nir Pilar[3], Shali Mazaki-Tovi[2], Hannah Kanety[1]
[1]*Institute of Endocrinology, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel*
[2]*Department of Obstetrics and Gynecology, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel*
[3]*Department of Cell and Developmental Biology, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel*

09:30 Placental Maternal and Fetal Vascular Circulation in Healthy Non Obese and Metabolically Healthy Obese Pregnant Women

Marina Shargorodsky[1,2], Jacob Bar[1,2], Michal Kovo[1,2], Letizia Shraiber[1,2]
[1]*Endocrinology, Wolfson Medical Center, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University , Tel Aviv , Israel, Israel*

09:42 The Impact of Glucose Variability on Fetal Growth in Type 1 Diabetes Women

Eran Ashwal[1], Elad Miron[2], Eran Hadar[2], Ronny Chen[2], Arnon Wiznitzer[2], Yoel Toledano[2]
[1]*Lis Maternity Hospital, Sourasky Medical Center, Israel*
[2]*Division of Maternal-Fetal Medicine, Helen Schneider Women's hospital, Rabin Medical Center-Beilinson campus, Israel*

08:30-10:00 Reproduction — Rimon Hall

08:30 Pediatricians` Attitudes and Beliefs towards Transgender Persons

Nitsan Landau[1], Uri Hamiel[2], Itay Tokatly Latzer[1], Elinor Mauda[1], Noa Levek[1], Liana Tripto-Shkolnik[3], Orit Pinhas-Hamiel[1]
[1]*Pediatric Endocrine and Diabetes Unit, Chaim Sheba Medical Center, Sackler School of Medicine, Tel-Aviv Unirversity, Ramat-Gan, Israel*
[2]*Pediatrics, Assaf Harofeh Medical Center, Sackler School of Medicine, Tel-Aviv Unirversity, Zerifin, Israel*
[3]*Endocrinology, Chaim Sheba Medical Center, Sackler School of Medicine, Tel-Aviv Unirversity, Ramat-Gan, Israel*

08:42 The N309K Pro-Protein Convertase Type 1 (PCSK1) Gene Mutation Causes Lack of Spontaneous Puberty and Primary Amenorrhea

Ulla Najwa Abdulhag, mona sharaf, Eran Lavi, Abdulsalam Abu Libdeh, David Zangen
Pediatric endocrinology, Hadassah Hebrew University medical center, Jerusalem, Israel

08:54 Hyperglycemia Affects the Pituitary Gonadotropes Directly, Altering the Epigenome and Lowering FSH Levels

Philippa Melamed, Ayah Saleh, Alona Feldman, Lilach Pnueli
Faculty of Biology, Technion-Israel Institute of Technology, Haifa, Israel

09:06 Reproductive activity of the adult female is affected by pre-pubertal immunological stress

Ben Bar-Sade[1], Or Eden[1], Reinhard Stoger[2], Gillian Bentley[3], Philippa Melamed[1]
[1]*Faculty of Biology, Technion - Israel institute of technology, Haifa, Israel*
[2]*School of Biosciences, University of Nottingham, Nottingham, UK*
[3]*Department of Anthropology, Durham University, Durham, UK*

09:18 Novel cyclic AMP-dependent mechanism mediates PGE2-induced FGF2 in bovine granulosa cells

Ketan Shrestha, Rina Meidan
Department of Animal Sciences, The Robert H. Smith Faculty of Agriculture, Food, and Environment, The Hebrew University of Jerusalem, Rehovot, Israel

09:30 Estrogen Suppresses Fibrosis in the Heart in Ovariectomized Mice – the Mouse Model of Human Menopause

Elishai Assayag[1], Irina Gurt[1], Einav Cohen-Kfir[1,2], Oran Yakobovsky[1], Donna Zfat-Zwas[3], Rivka Dresner-Pollak[1]
[1]*Endocrinology and Metabolism Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
[2]*Institute of Medical Research Israel-Canada, Hebrew University-Hadassah Medical School, Jerusalem, Israel*
[3]*Linda Joy Pollin Cardiovascular Wellness Center for Women, Division of Cardiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*

09:42 Hormonal Regulation of the Tet Enzymes in Developing Gonadotropes

Cfir David, Yahav Yosefzon, Anna Rabinovich - Tsukerman, Lilach Pnueli, Philippa Melamed
Biology, Technion - Israel institute of Technology, Israel

10:00-10:20 Coffee Break

10:20-10:30 Opening Session

10:30-11:20 Plenary lecture 1 Hall C

10:30 Calcium-Sensing Receptor (CaSR) Signaling Pathway Disorders

Raj Thakker
University of Oxford, UK

11:20-12:50 Symposia 1: Genome Editing (CRISPR) / iPS Hall C

11:20 Direct Conversion Approach and iPSCs for Disease Modelling and Future Cell-Based Therapy

Yossi Buganim
The Hebrew University-Hadassah Medical School, Jerusalem

11:50 Modeling of Beta-Cell Dysfunction through iPS Cells

Timo Otonkoski
Research Programs Unit, University of Helsinki, Finland, Jerusalem

12:10 Mechanisms of beta-cell Dysfunction in Permanent Neonatal Diabetes

Gil Leibowitz
Hadassah-Hebrew University Medical Center, Jerusalem

11:20-12:50 Symposia 2: Brain, Cognition and Type 2 Diabetes Hall B

11:20 Stroke and cognitive impairment in Diabetes and Pre- Diabetes

David Tanne

11:50 DNA Editing (CRISPR) in Alzheimer Disease

Dani Offen
Sackler School of Medicine, Tel Aviv University

12:10 The Role of type 2 Diabetes in Cognition and Associated Brain Damage

Michal Schnaider Beeri
Sheba Medical Center, Ramat Gan; The Icahn School of Medicine at Mount Sinai, NY

12:50-13:50 Lunch Break

13:50-14:40 Plenary lecture 2

13:50 The Endogenous Cannabinoid System - Looking Back and Ahead

Raphael Mechoulam
Medical Faculty, The Hebrew University, Jerusalem

14:40-16:10 Symposia 3: Update in Neuroendocrine Tumors and Beyond Hall C

14:40 New Pathways in the Treatment of Neuroendocrine Tumors

Marianne Pavel
Division of Endocrinology, Friedrich Alexander University of Erlangen-Nürnberg, Erlangen, Germany

15:05 Update in Carcinoid Syndrome

Simona Glasberg
NET Unit, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel

15:30 Swinging between Genotype and Phenotype in Von Hippel-Lindau Patients – What have we learned?

Auryan Szalat
Hadassah Medical Center, Jerusalem

14:40-16:10 Symposia 4 Cannabinoid Signaling in Metabolic Diseases and Aging Hall B

14:40 **Adipose cannabinoid CB1 receptor as key regulator of energy homeostasis**

Beat Lutz
Institute of Physiological Chemistry & German Resilience Center (DRZ) University Medical Center of the Johannes Gutenberg University Mainz

15:05 Diabesity-Induced Renal Dysfunction: Do Cannabinoids Contribute?

Yossi Tam
Faculty of Medicine The Hebrew University of Jerusalem

14:40 Age-dependent Effect of Cannabis on Cognitive Function

Andreas Zimmer

Institute of Mo lecular Psychiatry, University of Bonn, Germany

16:10-16:40 Honorary Ceremony

Arie Gertler
Introduction: Avraham Karasik

16:40-17:30 Meet the experts Hall C

Meet the experts: Diagnostic Challenges in Multiple Endocrine Neoplasia type 1 (MEN1): Usefulness of Genetic Analysis

Raj Thakker

University of Oxford, UK

MONDAY, APRIL 30, 2018

07:30-08:30 Registration and Gathering

08:30-10:00 Diabetes — Hall B

08:30 Morbidity and Mortality of Patients with Diabetes Mellitus Hospitalized for Infectious Diseases

Amit Akirov[1,2], Ilan Shimon[1,2], Alexander Gorshtein[1,2]
[1]*Beilinson Hospital, Institute of Endocrinology, Petach Tikva, Israel*
[2]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

08:42 Cannabinoid-1 Receptor Regulates Mitochondrial Dynamics and Function in Renal Proximal Tubular Cells

Adi Drori, Anna Permyakova, Joseph Tam
Obesity and Metabolism Laboratory, Institute for Drug Research, Faculty of medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

08:54 Metabolic Components More Prevalent Among Fragile X Premutation Women

Noah Gruber[1,2], Lilach Marom Haham[3], Shai Elizur[2,3], Yoram Cohen[2,3], Lidia Gabis[2,4], Yonit Banet Levi[4], Michal Berkenstadt[2,5], Liat Ries-Levavi[5], Orit Pinhas-Hamiel[1,2]
[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]*In-Vitro Fertilization Unit, Sheba Medical Center, Ramat Gan, Israel*
[4]*Child Development Center, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel*
[5]*Genetics Institute, Sheba Medical Center, Ramat Gan, Israel*

09:06 Leptin Antagonists as a Tool for Research and Therapy in Chronic Kidney Disease (CKD)

Robert H. Mak[1], Wai W. Cheung[1], Gili Solomon[2], Arieh Gertler[2]
[1]*Division of Pediatric Nephrology, Rady Children's Hospital San Diego, University of California, San Diego, USA, Mak Robert, San Diego, USA*
[2]*Institute of Biochemistry, Food Science and Nutrition,, Hebrew University of Jerusalem, Rehovot, Israel, Rehovot, Israel*

09:18 Diabetic Ketoacidosis among SGLT2i-Treated Patients: Insight from a Single Medical Center Located In the Region with the Highest Diabetes Mellitus Mortality Rate in Israel

Anat Jaffe, Naomi Dafni, Galit Haran
Endocrinology and Diabetes, Hillel Yaffe Medical Center, Hadera, Israel

09:30 The Relationship between Glucose Control & Functional Indices in Older People with Diabetes

Michal Azmon, Michal Azmon[1], Tali Cukierman-Yaffe[2], Tali Cukierman-Yaffe
[1]*Physical Therapy, Ariel University, Israel*
[2]*Endocrinology, Sheba Medical center, Tel Hashomer., Israel*

09:42 Food Restriction followed by Refeeding with a Casein- or Whey-Based Diet Differentially Affects the Gut Microbiota of Pre-Pubertal Male Rats

Galia Gat-Yablonski[1,2,4], Majdi Masarwi[1,2], Moshe Phillip[1,2,4], Hadas Isaac Solnik[3], Sima Yaron[3], Raanan Shamir[1,5], Metsada Pasmanic-Chor[6]
[1]*Department of Pediatrics, Sackler School of Medicine, Tel Aviv University,, Tel Aviv, Israel*
[2]*Department of Pediatrics, Felsenstein Medical Research Center, Petach Tikva, Israel*
[3]*Faculty of Biotechnology and Food Engineering, Technion - Israel Institute of Technology, Haifa,*
[4]*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*

[5]*Institute for Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*
[6]*Bioinformatics unit, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv,*

08:30-10:00 Bone- related Endocrine Mechanisms — Hall C

08:30 The Effect Of Various Phytonutrients On Bone Health In Both Human Osteoclasts And Osteoblasts Cultures

Alaa Nimer, Hilla Ovadia, Noa Fine, Marina Khanin, Yoav Sharoni
Clinical Biochemistry and Pharmacology, Ben-gurion University, Israel

08:42 Catch Up Growth, What Limits It?

Galia Gat-Yablonski[1,2,4], Majdi Masarwi[1,2], Raanan Shamir[1,2,3], Moshe Phillip[1,2,4]
[1]*Department of Pediatrics, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[2]*Department of Pediatrics, Felsenstein Medical Research Center, Petach Tikva, Israel*
[3]*Institute for Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*
[4]*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*

08:54 The Impact of a Fracture Liaison Service (FLS) On 6 and 12 Months Mortality After Hip Fracture

Uri Yoel[1], Lior Baraf[1], Vitaly Medvedovsky[1], Dayana Cohen[1], Tamar Eshkoli[1], Roni Gat[2], Yuval Mizrakli[2], Avital Blum[2], Vera Polischuk[3], Poliana Shamgar[2], Dvora Lieberman[4], Nisim Ohana[3], Victor Novack[2], Ethel Siris[5], Merav Fraenkel[1]
[1]*Endocrinology, Soroka University Medical Center, Beer- Sheva, Israel*
[2]*Clinical Research Center, Soroka University Medical Center, Beer- Sheva, Israel*
[3]*Orthopedics, Soroka University Medical Center, Beer- Sheva, Israel*
[4]*Geriatrics, Soroka University Medical Center, Beer- Sheva, Israel*
[5]*Division of Endocrinology, Columbia University Medical Center, New York, USA*

09:06 Vitamin D Supplementation Attenuates Hepatic Triglycerides Accumulation in Zebrafish Nonalcoholic Fatty Liver Disease (NAFLD) Model

Dalia David-Niv, Lihi Grinberg, Chen Shochat, David Karasik
The Azrieli Faculty of Medicine, Bar Ilan University, Safed, Israel

09:18 Trabecular Bone Score (TBS) Contributes to Bone Disease Assessment in Diabetic Patients

Michal Brodavka[2], Shmuel Stainlauf[2], Eyal Leshem[2], Shlomo Segev[3], Iris Vered[1], Roy Malka*[4], Liana Tripto-Shkolnik*[1]
[1]*Endocrine Institute, Chaim Sheba Medical Center, Israel*
[2]*Internal Medicine C, Chaim Sheba Medical Center, Israel*
[3]*Medical Screening Institute, Chaim Sheba Medical Center, Israel*
[4]*Innovation center, Chaim Sheba Medical Center, Israel*

09:30 Synergistic upregulation of VDR signaling and enhanced differentiation-inducing effects of the 19-nor D_2 analog PRI-5202 and Nrf2 activators in acute myeloid leukemia cells

Matan Nachliely[1], Boris Khalfin[1], Merav Cohen-Lahav[2], Andrzej Kutner[3], Michael Danilenko[1]
[1]*Department of Clinical Biochemistry & Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[2]*Laboratory of Biochemistry, Soroka University Medical Center, Beer Sheva, Israel*
[3]*Department of Chemistry and Department of Pharmacology, Pharmaceutical Research Institute, Warsaw, Poland*

09:42 Regulation of thioredoxin-interacting protein (TXNIP) by IGF1 signaling in Laron syndrome-derived cells

Karthik Nagaraj[1], Lena Lapkina-Gendler[1], Rive Sarfstein[1], Zvi Laron[2], Shoshana Yakar[3], Haim Werner[1]
[1]*Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[2]*Endocrine and Diabetes Research Unit, Schneider Children's Medical Center, Petah Tikva, Petah Tikva, Israel*
[3]*David B. Kriser Dental Center, Department of Basic Science and Craniofacial Biology, New York University College of Dentistry, New York, New York, USA*

08:30-10:00 Thyroid — Rimon Hall

08:30 High free T3 predict long survival

David Strich[1], Ariel Israel[2], Shalom Edri[3], David Gillis[4]
[1]*Pediatric Specialist Clinic, Clalit Health services, Jerusalem District and Shaare Zedek Medical Center, Israel*
[2]*Department of Family medicine, Clalit Health services, Jerusalem District, Israel*
[3]*Health Information, Clalit Health Services*
[4]*Pediatrics,, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*

08:42 Long Term Outcomes and Prognostic Factors in Patients with Differentiated Thyroid Cancer and Bone Metastases

Omer Slook[1], Sigal Levy[2], Ilana Slutzky-Shraga[1,3], Eyal Robenshtok[1,3], Gloria Tsvetov[1,3], Avner Lifshitz[1,3], Ilan Shimon[1,3], Carlos Benbassat[1,4], Dania Hirsch[1,3]
[1]*Tel-Aviv University, Sackler Faculty of Medicine*
[2]*Sackler Faculty of Exact Sciences, Tel Aviv University*
[3]*Endocrine Institute, Rabin Medical Center*
[4]*Endocrine Institute, Assaf Harofeh Medical Center, Zerifin*

08:54 Bone Marrow Suppression in Elderly Patients Following Empiric Radioiodine Therapy – Real-Life Data

Hadar Duskin Bitan[1,3], Anat Leibner[1], Oren Amitai[1], Dania Hirsch[1,3], Carlos Benbassat[2,3], Ilan Shimon[1,3], Eyal Robenshtok[1,3]
[1]*Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center, Petah-Tikva, Israel*
[2]*Endocrine Institute, Assaf Harofeh Medical Center, Israel*
[3]*Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel*

09:06 High Rate of Hearing Loss among Patients with Congenital Hypothyroidism

Tal Almagor[1,2], Dan Nachtigal[3], Zohara Sharroni[4], Ora Hess[1], Gadir Elias-Assad[1], Yardena Tenenbaum-Rakover[1,5]
[1]*Pediatric Endocrine Institute, Ha'Emek Medical Center, Afula, Israel*
[2]*Pediatric Department B, Ha'Emek Medical Center, Afula, Israel*
[3]*Department of Otolaryngology, Head and Neck Surgery, Ha'Emek Medical Center, Afula, Israel*
[4]*Department of Audiology, Ha'Emek Medical Center, Afula, Israel*
[5]*The Rappaport Faculty of Medicine, Technion, Haifa, Israel*

09:18 Diagnosing and Managing Multiple Endocrine Neoplasia type 1 (MEN1)-Related Pancreatic Neuroendocrine Tumors in Israel: A Specialist Center Experience

Inbal Uri, Benjamin Glaser, David J. Gross, Simona Grozinsky-Glasberg
Neuroendocrine Tumor Unit, Endocrinology & Metabolism Department, Division of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

09:30 Increased Risk of Antithyroid Drug-induced Agranulocytosis with Amiodarone

Michal Gershinsky[1,2,3], Idit Lavi[4], Chen Shapira[1,3], Naomi Gronich[4]
[1]*Endocrinology and Diabetes, Clalit Health Services, Haifa, Israel*

[2]*Endocrinology and Diabetes, Lady Davis Carmel Medical Center, Haifa, Israel*
[3]*Faculty of Medicine, Ruth and Bruce Rappaport, Technion - Israel Institute of Technology, Haifa, Israel*
[4]*Community medicine and epidemiology, Clalit Health Services, Haifa, Israel*

09:42 Reassessment of Differentiated Thyroid Cancer Patients Using the 8th TNM classification System: a comparative study

Carlos Benbassat[1], Limor Muallem Kalmovich[2], Keren Or[1], Shlomit Koren[1], Dror Cantrell[1], Miriam Shteinschneider[1]
[1]*Endocrine Institute, Assaf Harofeh Medical Center*
[2]*Head and Neck Surgery Unit, Assaf Harofeh Medical Center*

10:00-10:20 Coffee Break and Exhibition Visit

11:05-11:55 Plenary lecture 3 — Hall C

11:05 Precision Medicine, What is it and where is it going?

Jeffrey Alan Golden
Department of Pathology, Brigham & Women's Hospital, Ramzi S. Cotran Professor of Pathology, Harvard Medical School

11:55-13:25 General Assembly and Prizes session — Hall C

13:25-14:20 Lunch Break and Exhibition Visit

14:20-15:20 Symposia 5: Concept of Immunotherapy in Cancer — Hall C

14:20 Immune Checkpoint blockade in cancer therapy
Gal Merkel
Sheba Medical Center

15:00 Endocrine Complications of Cancer Immunotherapies

Rena Polak
Hadassah Medical Center, Jerusalem

14:20-15:20 Symposia 6: Treatment of Thyroid Disorders - A Different View — Hall B

14:20 Role of T3 in the Treatment of Hypothyroidism - The Deiodinase Story

Karen Tordjman
Sourasky Medical Center, Tel Aviv

14:20 Role of T3 in the treatment of hypothyroidism - Why, when and how?

Eyal Robenshtok
Rabin Medical Center, Beilinson campus

15:20-15:40 Coffee break and Exhibition Visit

15:40-15:50 Introduction: Avraham Karasik — Hall C

15:50-16:40 Plenary lecture 4 — Hall C

15:50 Integrating Genetics, Environment and the Microbiome in Pathogenesis of Diabetes and Metabolic Syndrome

C. Ronald Kahn
Joslin Diabetes Center, Harvard Medical School, Boston, USA

POSTERS

MONDAY, APRIL 30, 2018

10:20-11:05 Poster Session, Poster Hall - Hall A

1. **Three Meals Diet vs. Six Meals Traditional Diet, Improves Glucose Variability, Weight Loss and Total Daily Insulin dose in type 2 Diabetes**

   Daniela Jakubowicz[1], Oren Froy[2], Shani Tsameret[2], Julio Wainstein[1], Itamar Raz[3], Nava Chapnik[2], Tali Ganz[1], Miriam Menaged, Miriam Menaged[1], Naomi Mor[1], Mona Boaz[1], Yosefa Bar-Dayan[1], Zohar Landau[1]
   [1]*Diabetes Unit. Wolfson Medical Center, Tel Aviv University, Israel*
   [2]*Institute of Biochemistry, Food Science and Nutrition, The Hebrew University of Jerusalem, Israel*
   [3]*Diabetes Unit. Hadassah University Hospital, The Hebrew University of Jerusalem, Israel*

2. **Optoacoustic Imaging of Blood Oxygenation in FXIII Overexpressing Murine Placentae Reveals Decreased Hemoglobin Levels in Placental Circulation.**

   Sima Stroganov[1], TCP Sardella[2], Gadi Cohen[1], Roni Hadas[1], Reut Avni[1], Michal Neeman[1]
   [1]*Biological Regulation, Weizmann Institute of Science, Israel*
   [2]*Biological and Medical imaging, iThera Medical GmbH, Germany*

3. **GnRH Induces ERK-Dependent Bleb Formation in Gonadotrope Cells, Involving Recruitment of Members of a GnRH Receptor-Associated Signalosome to the Blebs**

   Liat Rahamim-Ben Navi[1], Anna Tsukerman[2], Alona Feldman[2], Philippa Melamed[2], Rony Seger[3], Zvi Naor[1]
   [1]*Department of Biochemistry and Molecular Biology, Tel Aviv University, Israel*
   [2]*Faculty of Biology, Technion-Israel Institute of Technology, Israel*
   [3]*Department of Biological Regulation, Weizmann Institute of Science, Israel*

4. **Neonatal Diabetes Mellitus Caused by a Novel *GLIS3* Mutation in Twins**

   Shira London[1], Gadir Elias-Assad[1,2], Marie Noufi-Barhoum[1,3,4], Clari Felszer[5], Marina Paniakov[5], Scott Vainer[5], Sarah Flanagan[6], Jayne Houghton[6], Yardena Tenenbaum-Rakover[1,2]
   [1]*Pediatric Endocrine Institute, Ha'Emek Medical Center, Afula, Israel*
   [2]*The Rappaport Faculty of Medicine, Technion, Haifa, Israel*
   [3]*Pediatric Health Center, Clalit Health Services, Naharia, Israel*
   [4]*Faculty of Medicine, Bar-Ilan University , Zeffat, Israel*
   [5]*Neonatal Intensive Care Unit, Ha'Emek Medical Center, Afula, Israel*
   [6]*Molecular Genetics, University of Exeter Medical School, Exeter, UK*

5. **The impaired inflammatory-angiogenic balance in ovaries of PCOS mice can be reversed by pigment epithelial-derived factor (PEDF)**

   Irit Miller[1], Hadas Bar-Joseph[1], Ido Ben-Ami[2], Ruth Shalgi[1]
   [1]*Department of Cell and Developmental Biology, Sackler Faculty of Medicine, Tel-Aviv University, Israel*
   [2]*IVF and Infertility Unit, Department of Obstetrics and Gynecology, Assaf Harofeh Medical Center, Israel*

6. **Let`s Talk about It- Addressing Sexual Dysfunction in Diabetes**

   Asia Klein[1], Liora Valinsky[2], Liana Tripto-Shkolnik[1], Yael Yiftah[1], Yoel Toledano[2]
   [1]*Central District Management, Meuhedet*
   [2]*Division of Medicine, Meuhedet*

7. **Which Predictors Differentiate between Obese Children and Adolescents with Metabolic Complications and Those Who are Metabolically Healthy Obese (MHO)?**

   Shlomit Shalitin[1,3], Michal Yackobovitz-Gavan[1,3], Moshe Phillip[1,3], Merav Gil[2]
   [1]*The Jesse Z. and Lea Shafer Institute of Endocrinology and Diabetes, Schneider Children's Medical*

Center of Israel, Israel
[2]*Pediatric Department A, Schneider Children's Medical Center of Israel, Israel*
[3]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

8. **Does a First-Degree Family History of Diabetes Impact Placental Maternal and Fetal Vascular Circulation and Inflammatory Response?**

Marina Shargorodsky
Endocrinology, Wolfson Medical Center, Israel
Sackler Faculty of Medicine,, Tel Aviv University, Tel Aviv, Israel, Israel

9. **Managing Low Testosterone In Aging Males: A Survey Of Clinical Practice Patterns Among Endocrinologists And Urologists In Israel**

Avraham Ishay[1], Sharon Tzemah[2], Michael Cohen[3]
[1]*Endocrinology, Haemek Medical Center, Israel*
[2]*Urology, Haemek Medical Center, Israel*
[3]*Urology, Haemek Medical Center, Ivory Coast*

10. **Effect Of Pre-gestational Weight And Gestational Weight Gain In Women With Gestational Diabetes Controlled With Medication On Pregnancy Outcome- Is Recommended Weight Gain Too Liberal?**

Ronit Koren[1,2,5], Yuval Hochman[1,5], Shlomit Koren[3,5], Tomer Ziv-Baran[4,5], Yifat Wiener[2,5]
[1]*Department of Internal Medicine A, Assaf Harofeh Medical Center, Zerifin, Israel*
[2]*Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Assaf Harofeh Medical Center, Israel*
[3]*Diabetes unit, Assaf Harofeh Medical Center, Zerifin, Israel, Israel*
[4]*Department of Epidemiology and Preventive Medicine, School of Public Health, Israel*
[5]*Sackler Faculty of Medicine, Tel-Aviv University, Israel*

11. **Metabolic Changes in Patients with Multiple Myeloma**

Efrat Markus[1], Svetlana Trestman[2], Irit Avivi[2,3], Naftali Stern[1,3], Elena Izkhakov[1,3]
[1]*Institute of Endocrinology, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center, Israel*
[2]*Institutes of Hematology, Tel Aviv Sourasky Medical Center, Israel*
[3]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

12. **Identification of ZYG11A as a Novel Metabolic Target for IGF1 Action in Endometrial Cancer Cells**

Laris Achlaug[1], Karthik Nagaraj[1], Rive Sarfstein[1], Lena Lapkina-Gendler[1], Zvi Laron[2], Ilan Bruchim[3], Haim Werner[1]
[1]*Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Israel*
[2]*Endocrine and Diabetes Research Unit, Schneider Children's Medical Center, Israel*
[3]*Gynecological-Oncology Division, Hillel-Yaffe Medical Center, Israel*

13. **Disease Presentation and Remission Rate in Graves` Disease Treated with Anti-Thyroid Drugs: Is Gender Really a Factor?**

Talia Diker Cohen[1,2], Hadar Duskin-Bitan[1,2], Ilan Shimon[1,2], Dania Hirsch[1,2], Amit Akirov[1,2], Gloria Tzvetov[1,2], Eyal Robenshtok[1,2]
[1]*Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center – Beilinson Hospital, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

14. **Cushing`s Syndrome: Comparison between Cushing`s Disease and Adrenal Cushing`s**

Dania Hirsch[1,2,3], Ilan Shimon[1,2], Yosef Mansiterski[2,3], Nirit Aviran-Barak[2,3], Oren Amitai[1,2], Vered Kopel[4], Varda Nadler[4], Sandra Alboim[4], Gloria Tsvetov[1,2,3]
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15. Bone mineral density (BMD) in people living with HIV evalution by Quantitative UltraSonometry (QUS)- a pilot study.

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16. Bilateral Medullary Thyroid Carcinoma in a 3-Year-Old Female Patient with MEN 2A Syndrome Undergoing Prophylactic Thyroidectomy: Should Current Guidelines Be Revised?

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17. Pediatric Type 1 Diabetes Mellitus Incidence and Airborne Particulate matter in Israel

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18. Multifocality in Differentiated Thyroid Cancer (DTC) is Associated with More Severe Disease but unlikely to be an Independent Prognostic Factor

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19. Hypothyroidism And Hyperthyroidism Swings Due To Thyroid-receptor Antibodies During Three Consecutive Pregnancies

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20. Transcriptomic profiling of bovine corpus luteum maturation

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21. Crouzon`s Syndrome and Polyglandular Autoimmune Disease

Viviana Ostrovsky, Taiba Zornitzki, Tal Schiller, Nitza Vazana, Hilla Knobler
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22. Health lifestyle and obesity of adult patients with Congenital Isolated Growth Hormone Deficiency treated in childhood.

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23. Tumor Induced Osteomalacia: An Elusive Diagnosis

Afif Nakhleh[1], Elena Segal[1], Michal Weiler-Sagie[2], Ahmad Khatib[1], David Nikomarov[3], Rostislav Novak[3], Rina Hemi[4], Eugene Vlodavsky[5], Naim Shehadeh[1]
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24. Prevalence of Diabetes Mellitus Among Children Treated with Growth Hormone in Israel

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25. Transgenic *Drosophila* Lines Expressing a Constitutively Active Human LH Receptor Variant (LHR^{D578Y}) in the Gonads Exhibit a Decreased Fecundity

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26. Head Circumstances, Birth Length, and Weight of Neonates of Mothers with Hypothyroidism

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27. New Insights Into the Pathogenesis and Treatment of Polycystic Ovary Syndrome - The Role of Pigment Epithelium-Derived Factor (PEDF)

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28. Insulin Detemir use is associated with higher occurrence of hypoglycemia in hospitalized patients with hypoalbuminemia

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29. Mcm2 Expression in Adrenocortical Tumors

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30. Thyroid Dysfunction in Melanoma Patients Treated with Anti PD-1 Therapy

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31. Differential Effects OF INSR and IGF1R on ERK and AKT Signaling Pathways in Breast Cancer Cells

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32. Adrenal insufficiency in hospitalized patients with hyponatremia

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33. Circannual Variability of Thyroid Axis Function, Based Upon TSH Results from Hypothyroid Treated and Healthy Individuals Over Time

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34. Primary hyperparathyroidism in the elderly

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35. Recombinant zebrafish (*Danio rerio*) and rainbow trout (*Oncorhynchus mykiss*) recombinant growth hormones – preparation and bioactivity

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36. Bilateral Massive Adrenal Hemorrhage Causing Acute Adrenal Insufficiency in a Patient With Emergency Hypertension

Yohai Shraga[1], Gal Cohen[1], Carmi Bartal[2], Muhamad Ahasla[2], Odelya Peretz[2], Dayana Cohen Kobi[3], Uri Yoel[3], Lior Baraf[3], Merav Fraenkel[3]
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37. Differential roles of PKC isoforms (PKCs) in GnRH stimulation of MAPK phosphorylation in gonadotrope derived cells

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38. A comprehensive intervention for promoting successful aging amongst below the cognitive norm older people with diabetes- a feasibility study.

Tali Cukierman-Yaffe, Michal Azmon, Rachel Natovich, Omri Gury-Twito, Svetlana Rudui, Tomer Yair, Noa Gayus

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39. Our preliminary experience with sonography-guided percutaneous ethanol injection treatment for recurrent symptomatic thyroid cysts

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40. Our Experience with rPTH (1,84) in Two Patients with Hypoparathyroidism

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41. Impact of Support Group Sessions On Knowledge and Glycemic Control Among Patients With Type 2 Diabetes. A randomized, Placebo-Controlled Trial.

Avraham Ishay, Hila Kfir, Simha Amar, Ada Khalif, Reut Shefer, Elena Chertok -Shaham
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42. Life changing decisions due to precise diagnosis in families of children with Maturity Onset Diabetes of the Young (MODY).

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43. Influence of Ethnicity on Gestational Diabetes Mellitus in the Center of Israel: A Retrospective Cohort Study

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44. Congenital Hypothyroidism due to TSH resistance, a Spectrum of a Disease

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45. Involvement of the endocannabinoid system in the metabolic response of adipose tissue in postpartum dairy cows

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46. Hypophosphatasia: Rare metabolic bone disease with high burden of illness in adulthood

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47. Short term adherence with discharge recommendation for insulin treatment among patients with type 2 diabetes

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48. Incidence of Glucocorticoid Induced Hyperglycemia among Hospitalized Nondiabetic Patients

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49. Prevalence of Unexplained Anemia and Associated Clinical Parameters in Diabetes and Pre-Diabetes

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50. High Fracture Susceptibility with Increased Frequency of Hip Fractures in Patients with Hypoparathyroidism

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51. Effect of short-term intervention by an interdisciplinary team of diabetes specialists on glycemic control in patients with uncompensated diabetes (HbA1C ≥9%) in a community setting

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52. The Effect of CAG Repeats Length on Differences in Hirsutism Among Healthy Israeli Women of Different Ethnicities

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53. Metastatic Papillary Thyroid Carcinoma Resembling Spinal Ependymoma

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54. Rates of Malignancy in Cytology Indeterminate Thyroid Nodules- A Single Center Surgical Series

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55. Sexual Dimorphism of Size: Ontogeny and Life History

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56. Early Growth in Relation to Family Size and Birth Rank

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57. Economic Evaluation of Dapagliflozin as Add-on to Metformin for T2DM Treatment in the Israeli Healthcare Setting

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58. Lipid Profile in Youth with T1DM: Evaluating Factors Contributing To Dyslipidemia

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59. Fracture Risk in Patients with Acute Poliomyelitis Going Through Late Adulthood

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60. Long-Term follow up of Monthly Somatostatin Analogues Therapy in Pediatric Hypothalamic Obesity Patients

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61. Topical Application of an Aqueous Nasal Steroids Solution as Effective and Safe in the Management of Skin Irritation Due to Continuous Glucose-Monitoring System Adhesives

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ABSTRACTS

Efficacy and Safety of Long-acting Pasireotide in Acromegaly: A Multicenter Study

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Pasireotide, a multi-receptor-targeted somatostatin analogue (SSA) with high affinity for $SSTR_5$ was recently approved for the treatment of active acromegaly.

Aim and Methods: A multicenter (7 centers) retrospective study was conducted in Israel to investigate the efficacy and safety of long-acting (LAR) pasireotide treatment in patients with acromegaly.

Results: The cohort included 34 patients (19 males) with acromegaly (28 macroadenomas). Mean baseline IGF-1 at diagnosis was 3.1±1.3 X ULN. All but five patients have undergone pituitary surgery and six received sellar radiotherapy. All remained with active acromegaly despite SSA treatment. Immediately before pasireotide-LAR initiation 21 patients were under SSA monotherapy, pegvisomant (n=2) or combination therapy of SSA with pegvisomant (n=9). Two were untreated. Mean IGF-I was 1.8±0.9 ULN before switching to pasireotide. Pasireotide-LAR starting dose was 40 mg/month in most patients. IGF-1 normalization was achieved in 19 patients, IGF-1 between 1-1.2 x ULN was reached in three, and in additional three patients IGF-1 was significantly suppressed. No effect was seen in nine patients. Pasireotide dose was reduced by 20 mg in six patients with excellent response, with preserved IGF-1 control in four. Severe headaches in six patients disappeared or significantly improved with pasireotide. Side effects consisted of symptomatic cholelithiasis in one patient and impairment of glucose control in 17 patients, requiring initiation or intensification of antidiabetic treatment in ten. One patient developed diabetic ketoacidosis, two months following pasireotide discontinuation.

Conclusions: In the real-life scenario ~56% of patients with acromegaly resistant to first-generation SSA, may achieve IGF-1 normalization with pasireotide treatment.

A Single Parameter or Combination of Parameters for Predicting an Adequate Response to The Short Synacthen Test in Hospital

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Introduction The short Synacthen test (SST) is widely used to assess the hypothalamus pituitary axis (HPA) especially in the outpatient setting. In the inpatient setting however, technical difficulties to adhere to the protocol may pose a challenge for using this test.

Aim In the current study we attempted to find a parameter or a combination of simple parameters that may improve the ability to predict an inadequate response to the SST without conducting such a test.

Methods Information was retrieved retrospectively from 197 medical patients who had had a 250 mcg SST to exclude adrenal insufficiency (AI) between the years 2000-2012 at the Shaare Zedek Medical Center. Basal serum cortisol (BSC), sodium, potassium, glucose, creatinine, TSH, hemoglobin, eosinophil and lymphocyte counts as well as blood pressure values were evaluated for a correlation with the results of the SST.

Results A BSC of 280 nmol/l (10.15 mcg/dl) provides a negative predictive value (NPV) of 94% for AI. We did not find a combination of parameters that were able to improve the prediction of AI without conducting a SST.

Conclusions in this study the only parameter that predicted the results of a SST was the BSC. A BSC of 280 nmol/l (10.15 mcg/dl) or above makes the diagnosis of AI very unlikely and in such a case precludes the need for a SST.

A New Form of Selective Hypoaldosteronism: Aldosterone Failure to Respond to ACTH is Linked to Glucocorticoid Excess, Normal Cortisol Response to ACTH and Unexplained Malaise

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Background: Aldosterone (aldo) has been recently characterized as a "stress hormone", rising in response to stress and, in parallel, to very low/low doses (0.03-1ug, IV) of ACTH.

Aim: We set out to determine whether or not the aldo response to a low dose of ACTH may be selectively impaired in humans.

Methods: We tested the aldo response in 118 consecutive subjects referred for the low dose (1ug) ACTH test due to suspected hypocortisolism and/or unexplained weakness. Lack of aldo response was defined as a rise 4ng/dl, as defined for the diagnosis of hypoaldosteronism by the 250ug ACTH dose test.

Results: Twenty-three subjects had low/no-aldo response, 11 of whom had used exogenous glucocorticoids, and 2 had former Cushing disease. Surprisingly, the cortisol response to ACTH was impaired in only 2 of these patients. Impaired aldo response to ACTH was also found in 6 subjects with hypothyroidism, 2 with orthostatic hypotension, 1 with non-functioning pituitary macroadenoma and 1 F to M transgender. Overt hyperkalemia was not seen, but 2 subjects had moderate renal failure. Hyponatremia was seen in 5 subjects, who all showed a normal cortisol response.

Conclusion: Blunted aldo response to ACTH is 1) not rare;2) seen mostly in subjects exposed to glucocorticoid excess who nevertheless maintain a normal cortisol response to ACTH 3)patients with hypothyroidism and/or orthostatic hypotension; 4) linked to hyponatremia and malaise, but not hyperkalemia. Whether or not low dose mineralocorticoid replacement therapy might be beneficial in this patient population is presently under study.

Primary Treatment of Nonfunctioning Pituitary Adenoma With D2 Agonists- A Single Center Experience

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Background

Trans-sphenoidal surgery is the standard treatment of nonfunctioning pituitary macroadenoma (NFPMA). Recently, D2 agonist (D2A) have been shown to decrease rates of remnant growth and need for repeat surgery or radiotherapy in NFPMA. The role of primary medical treatment of NFPMA is unknown.

Aim

To report our experience with D2A as primary medical treatment for NFPMA.

Methods

17 patients with NFPMA who received primary treatment with D2A, without prior surgery, were retrospectively evaluated. Pituitary function tests, clinical parameters and imaging were assessed prior and after D2A treatment.

Results

Mean age was 68.5±10.2 years, 59% were males. Forty seven percent presented with headache. None had visual field defects. At baseline rates of secondary adrenal insufficiency, central hypothyroidism and GH deficiency were 0, 17.6 and 23.5% respectively. Mean baseline tumor height and width on MRI were 19.6± 6.4 and 18.7±8.5 mm respectively. Mean cabergoline dose was 1.6 mg per week. Median D2A treatment duration was 35.7 months (range 9-140). Tumor height and width on MRI decreased in 69% and 63% of patients respectively. The distance between the tumor and the optic chiasm decreased in 50% and increased in none. During follow up 2 patients under medical treatment were operated due to tumor growth and evolving visual fields defect.

Conclusions

In our institutional cohort of patients with NFPMA, primary treatment with D2A decreased tumor size and eliminated the need for surgery in most patients. Further long term assessment of this medical treatment approach for NFPMA is needed.

Favourable Outcomes of Peptide Receptor Radionuclide Therapy (PRRT) for Treatment of Metastatic Rectal Neuroendocrine Neoplasia (NEN)

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Background Metastatic disease from rectal NEN are less common than other NEN origins and carries a poor prognosis. Treatment evidence for such patients (pts) is lacking.

Aim To assess PRRT outcomes in pts with somatostatin receptor (SSTR) positive metastatic rectal NEN from 2 referral centres.

Methods Pts treated with PRRT were retrospectively reviewed. Anatomical imaging (RECIST 1.1), SSTR imaging response and toxicity were assessed 3 months post-PRRT. Kaplan-Meier estimate was used to determine PFS and OS from start of PRRT.

Results 23 consecutive pts (M=17, age 31-81yo) were reviewed. The majority (15 pts, 65%) had ENETS grade 2 disease, three had grade 3, one had grade 1, and 4 unavailable. 22 pts were treated for disease progression. Most had ^{177}Lu-DOTA-octreotate with median cumulative activity of 30 GBq, median 4 cycles. 13/23 pts had radiosensitising chemotherapy (5FU or capecitabine). At 3 months post-PRRT, disease control rate (DCR) was 96%: 57% (13/23) partial response and 39% stable disease. The median PFS was 29 months. Nine pts died, with median overall survival 76 months, median follow-up of 65 months. 15 pts had further treatments after initial PRRT (10 had further PRRT). Two patients had grade 3 lymphopenia, without significant renal toxicity, MDS or leukaemia. Of note, follow-up data on 4 extra pts completing treatment will be updated.

Conclusion Our results indicate high efficacy and morphologic responses with minimal toxicity and very encouraging survival from PRRT in patients with metastatic rectal NEN, particularly given the adverse prognostic features of this cohort.

Dysglycemia in Non-functioning Pancreatic Neuroendocrine Tumors (PNET): A New Form of Type 3c Diabetes Mellitus?

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Background Diabetes mellitus (DM) secondary to pancreatic diseases, termed type 3c DM. Cases were associated with chronic pancreatitis, pancreatic cancer, hemochromatosis, pancreatic resection cystic fibrosis , but not with NF-PNETs. Here we set out to determine whether or not NF-PNETs are associated with DM/dysglycemia.

Methods: Retrospective study to evaluate the rate of dysglycemia/DM in a cohort of NF-PNETs.

Results 100 consecutive patients: reviewed (F/M 31/69) with histologically confirmed NF-PNETs . Seventy subjects (70%) had abnormal glucose metabolism: overt DM in 35% (35) and impaired fasting glucose (IFG) in 35 subjects. The clinical correlates of NF-PNET with vs. without DM/IFG, respectively, were: older age (63±11; 53±15; p0.0002); localization at the pancreatic tail (58% vs. 33%); somewhat higher rate of pancreatic surgery (22 in all, of whom 17[77%] had DM/IFG); similar BMI (27±6; 28±5 kg/m2) and tumor size (2.6±0.5 vs. 3±0.5cm). DM/IFG combined patients fasting glucose was 118±26.1mg/dl, HBA1c 6.6±1.5%. The rate of DM in Israeli population at this cohort`s age is 13.5% according to Israeli Ministry of Health survey (vs. 35% in our NF-PNET cohort).

Conclusion: This is the first report of a high rate of impaired glucose metabolism, DM or IFG, in a cohort of NF-PNETs. The high prevalence of diabetes/pre-diabetes was not related to obesity or surgery alone, though each could have a contributory role. This finding this observation should prompt re-examination of the term "non-functioning" in the context of PNET and/or raise the possibility of increased rate of "NF"-PNETs in type 2 diabetes/pre-diabetes.

Obesity Among Children and Adolescents with Non-Classic Congenital Adrenal Hyperplasia Due to21-Hydroxylase Deficiency

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***Background*:** Higher rates of obesity were reported in patients with classical congenital adrenal hyperplasia, but little is known about adiposity among patients with non-classical congenital adrenal hyperplasia (NCCAH).

Aim: To assess the prevalence of overweight, obesity and cardio-metabolic risk factors among NCCAH patients.

Methods*:* A cross-sectional retrospective study of 114 NCCAH patients (93 females; mean age at assessment 17.1±6.9 years) diagnosed before age 18. Clinical assessment included anthropometric measurements, body composition (bio-impedance, waist-to-hip ratio) and blood pressure. Laboratory evaluation included fasting glucose, insulin, and lipid profile. Prevalence of overweight/obesity was calculated for the entire cohort. Data of patients in grades 7-12 (n=76) were compared to those of the National Health and Nutrition Survey (Mabat 2015-2016, grades 7-12).

Results: For the entire cohort rates of overweight and obesity were 21.9% and 11.4% respectively. Prevalence of obesity or obesity+overweight for patients in grades 7-12 was comparable to that in the Israeli population (10.5 vs. 15.1% p=0.24, 34.2 vs. 41.6% p=0.18). No significant difference was found between treated (n=76) and untreated patients (n=38) in any of the metabolic or anthropometric parameters except for lower fat mass in treated patients: fat in percent of body weight 21.4±8.3 vs. 27.8±6.8, p=0.02.

Longer duration of steroid treatment was associated with increased systolic (r=0.26, p0.05) and diastolic (r=0.31, p0.01) blood pressure and with hip circumference (r=0.54, p0.0005) but inversely related with BMI-SDS

(r= -0.20, p0.05).

***Conclusion*:** NCCAH diagnosed in childhood (treated or untreated) is not associated with increased risk of overweight, obesity or metabolic derangements.

Oral Presentations: Diabetes Mellitus

The RNA Binding Protein PTBP1 is a Key Regulator of Gluconeogenesis

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Aim: Liver plays a key role in maintaining glucose homeostasis. The RNA binding protein polypyrimidine tract binding protein (PTBP1) was found to be significantly upregulated in liver of obese-diabetic mice. As PTBP1 plays an important role in many aspects of RNA processing including alternative-splicing, mRNA stability and translational regulation, we assessed its role in the regulation of metabolic homeostasis.

Methods: To establish PTBP1 significance to metabolic homeostasis, its expression in C57BL/6 mice liver and in primary hepatocytes was downregulated using adenoviral delivery of shPTBP1. Ad-GFP served as control. Microarrays, qPCR, and bioinformatics experiments were used to identify mRNAs differentially expressed between control and hepatic-depleted PTBP1. IPGTT was used to evaluate glucose intolerance.

Results: We identified 109 genes differentially expressed in liver of fasted PTBP1-depleted mice. Among these, a significant decrease was observed in the gluconeogenic pathway rate-limiting enzymes; G6pase (glucose-6-phosphatase), PEPCK (phosphoenolpyruvate-carboxykinase-1), Fbp1 (fructose-bisphosphatase-1), and in HNF4a, a master transcriptional regulator of PEPCK and G6pase. Expression of Mir-107, known to impair insulin-signaling, was also significantly reduced. PTBP1 depletion was associated with improved glucose tolerance. Importantly, PTBP1 reduction in primary hepatocytes, impaired HNF4a but not PEPCK and G6Pase mRNA expression. However, under conditions which mimic the *in-vivo* fasting state (incubation with forskolin and dexamethasone), a marked induction in PEPCK and G6Pase mRNA levels was observed in the control but not in the PTBP1-depleted hepatocytes.

Conclusions: Our results point to PTBP1 as an important regulator of gluconeogenesis, and suggest that increase in its expression may alter hepatic physiology during obesity and diabetes.

Maturity Onset Diabetes of the Young 2 (MODY2): Insight from an Extended Family

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Introduction: MODY2 is a monogenic diabetes, caused by loss-of-function mutation in the glucokinase gene (*GCK*), and commonly presenting with mild fasting hyperglycemia without diabetes complications. **The aim** of our study was to assess the clinical outcome of MODY2 in a large cohort of patients from the same family living in the same village.

Methods: Clinical and biochemical data were collected from the medical records of 162 patients (66 Male) enrolled in the study. All patients underwent molecular analysis for the identified *GCK* mutation. **Results:** A novel missense mutation (c1278-1286del) was identified in *GCK*. Of 162 participants, 42 were positive for the identified mutation (MODY2), 39 were negative with Diabetes Mellitus type 2 (DMT2) and 81 were negative without DM. Over the years, the levels of glucose and HbA1c increased significantly (mean glucose 133 vs. 146 mg/mL and mean HbA1c 6.94 vs. 8.16%) in MODY2 patients. The increase in HbA1c was shown in obese, but not normal-weight patients. HbA1c values were significantly higher in normal-weight DMT2 compared to MODY2 patients (11.9 vs. 6.8%), but not in obese patients (10.0 vs. 8.43%). Diabetic complications were found in 25% of MODY2 patients compared to 50% of DMT2 patients.

Conclusions: Although MODY2 commonly has a benign course, our findings indicate that weight gain over the years is a risk factor for increased HbA1c, with the need for medical intervention and a risk of diabetes complications. These findings emphasize the importance of molecular genetic analysis and the need for long-term follow-up in patients with MODY2.

Involvement of Nitric Oxide and Endothelin Systems in the Pathogenesis of Endothelial Dysfunction in Diabetes

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Background: Endothelial dysfunction (ED) is a key feature of diabetes. Diabetic patients who also exhibit hyperlipidemia suffer from accelerated vascular complications. While the deleterious effects of high glucose levels (HG) and hyperlipidemia alone on ED is well established, the effects of combined hyperlipidemia and HG has not been thoroughly studied. Therefore, the current study examines**,** whether HG and hyperlipidemia exerts synergistic ED**.**

Methods: Incremental doses of glucose in the presence or absence of oxLDL were added to cultured macrovascular human umbilical vein endothelial cells (HUVECs) and human microvascular endothelial cell line (HMEC-1) cells. After 5 days, the status of nitric oxide (NO) and endothelin (ET)-1 systems as well as their signal transduction were assessed using western blot, ELISA and immunoreactive staining.

Results: Both microvascular and macrovascular endothelial cells exposed to HG and Ox-LDL or combination of both displayed enhanced ET-1 production. Overproduction of ET-1 stems from upregulation of Endothelin Converting Enzyme (ECE)-1 as observed under these conditions. In contrast, combination of HG and Ox-LDL dramatically decreased both total endothelial NO synthase (eNOS) by 60%, and activated eNOS (peNOS) by 50%. Moreover, Nrf2 (transcription factor for various antioxidant enzymes) decreased by 42% and its active form (pNRF2) by 56%, as compared to baseline. Likewise, Endothelin Receptor B ($ET_{B)}$ levels on endothelial cells decreased by 64% from baseline.

Conclusions: Combined diabetes and hyperlipidemia is characterized by activation of the ET system and attenuated eNOS and Nrf2 level/activity. These findings suggest that perturbations in these paracrine systems may contribute to diabetic endothelial dysfunction.

A Randomized Controlled Trial Comparing a Telemedicine Therapeutic Intervention with Routine Care in Adults with type 1 Diabetes Mellitus Treated by Insulin Pumps

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Objective: To examine the effectiveness and safety over a 12-month period of a telemedicine intervention in adults with type 1 diabetes treated with insulin pumps.

Research design and methods: Individuals with type 1 diabetes duration ≥1 year (mean±SD 19.5±11.5 years) and $HbA1_c$ ≥6.5% (≥ 48 mmol/mol) were randomized to a telemedicine or standard care group. Those in the intervention group were instructed to download data from insulin pumps and glucometers monthly. They received immediate phone feedback and recommendations for insulin dose adjustment as needed; and face-to-face visits once in 6 months (3 in 12 months), compared to once every 3 months (5 in 12 months) for the standard care group.

Results: The mean age was 41.5±13.5 years; 47.5% were male; the mean HbA_{1c} was 7.8±0.6% [62±7.2 mmol/mol]. HbA_{1c} changes were -0.09% and -0.07% in the intervention (N=28) and control groups (N=33), respectively (p=0.99) at 6 months; and -0.143% and 0.03% (p=0.29) at 12 months. Treatment satisfaction and quality of life scores were similar in both groups, although a positive trend was seen in the intervention group. Direct total costs were 24% less in the intervention group, and indirect total costs decreased by 22% compared to the year preceding the study.

Conclusion: Internet-based insulin dose adjustment is as effective and safe as routine care in adults with type 1 diabetes treated by insulin pumps. For suitable patients, some of the time-consuming routine visits may be replaced by user-friendly digital medicine.

MicroRNA Expression Profile in Human Visceral and Subcutaneous Adipose Tissues during Pregnancy: Implications for Metabolic Adaptations to Normal Gestation and Putative Mechanism in Gestational Diabetes

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Aim: MicroRNAs (miRNAs) are small noncoding RNAs that modulate gene expression. In adipose tissue miRNAs regulate adipocytes differentiation, metabolic and endocrine functions. The aim of this study was to compare miRNAs expression profile in visceral (VAT) and subcutaneous (SAT) adipose tissues between pregnant and non-pregnant women.

Methods: miRNA expression profile from paired VAT and abdominal SAT was characterized using NanoString nCounter technology in 3 groups: Non-pregnant (n=4) and pregnant (n=8) women and patients with gestational diabetes mellitus (GDM) requiring insulin treatment (n=6). Bioinformatics was employed to detect differentially expressed miRNAs. Results were validated using qPCR for selected miRNAs and miRNA-regulated genes.

Results: Expression differences were notable in VAT: 4 differentially expressed miRNAs were detected between normal-pregnant women and patients with GDM, 2 between normal-pregnant and non-pregnant women and 14 between GDM and non-pregnant women. In SAT, number of differentially expressed miRNAs among the three groups was 3, 1 and 2, respectively. miR-221-3p, miR-222-3p, miR-424-5p were overexpressed and miR-574-3p was underexpressed in VAT of GDM patients compared to non-pregnant women. miR-551b-3p was underexpressed in VAT of GDM patients compared to normal-pregnant women. qPCR analysis in a larger cohort validated findings for miR-221-3p, miR-222-3p and several of their putative genes.

Conclusions: miRNA expression profile of visceral and subcutaneous fat depots reveals pregnancy- and GDM-related distinctive pattern, most notably in VAT. Both miR-221 and miR-222 have been implicated in adipose tissue oxidative stress, inflammation, lipid and glucose metabolism providing putative mechanisms in the adaptation to normal gestation as well as to GDM.

Placental Maternal and Fetal Vascular Circulation in Healthy

Non-Obese and Metabolically Healthy Obese Pregnant Women

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Background: We investigated placental histopathology for lesions that are associated with maternal and fetal circulation abnormalities in obese pregnant women with and without metabolic alterations.

Methods: 332 pregnant women were divided into three groups: Group 1 included 163 non-obese metabolically healthy (NOMH); Group 2 included 106 obese metabolically healthy (OMH); Group 3 consisted 63 obese metabolically abnormal (OMA) subjects.

Results: Fetal vascular supply (FVS) abnormalities and Willous maturation defect (WMD) rate were higher in obese subjects without metabolic abnormalities, compared to NOMH subjects (p

Conclusion: We demonstrated that obesity, per se, is associated with an increased rate of placental vascular supply abnormalities and had a more adverse effect on fetal vascular circulation than on maternal vascular supply.

The Impact of Glucose Variability on Fetal Growth in Type 1 Diabetes Women

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Aim: Diabetes in pregnancy with poor glycemic control may cause an abnormal fetal growth. Thus, we explored the association of glucose variability and fetal growth in pregnant women with type 1 diabetes.

Methods: A retrospective cohort study of consecutive pregnant women with type 1 diabetes mellitus (T1DM) was performed. Eligibility criteria included a singleton pregnancy and continuous glucose monitoring for at least one month in each trimester. The association between glycemic variability, in terms of standard deviation (SD) and coefficient of variation (CV), and aberrant fetal growth (large for gestational age (LGA, 90th centile)) was analyzed.

Results: Overall, T1DM 51 women were included. Mean maternal age was 32.7±4.5 years. Mean pre-pregnancy HbA1C was 6.9±0.9%. Mean gestational age was 36.7±1.8 week, with an induction rate of 44.1%. Mean birthweight was 3,350±646g. Rate of LGA was 37.3%. Using ROC curve analysis, the predictive accuracy of MBG, SD, CV in every trimester for LGA neonates was analyzed. Of all, only the SD and CV in the 3rd trimester were found significant. In a multivariate logistic regression, controlling for time interval since diabetes was diagnosed, BMI, gestational weight gain, MBG, HbA1C and total daily dose of insulin during the 3rd trimester, SD and CV were significantly and independently associated with an increased risk for LGA (OR=1.18, 95% CI 1.02-1.39).

Conclusions: Aberrant glycemic variability in pregnant women with T1DM is significantly associated with an increased risk for LGA. We suggest to monitor glucose variability indices during those gestations in order to ensure normal fetal growth.

Oral Presentations: Reproduction

Pediatricians` Attitudes and Beliefs towards Transgender Persons

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Introduction: Pediatricians are becoming key figures for gender dysphoric persons, as the number of children seeking information or treatment for gender dysphoria rises. Furthermore, initiation of treatment during a narrow time window in childhood has physical and emotional benefits and is now considered standard of care. A barrier that can preclude appropriate care is pediatricians' attitudes towards transgender. Little is known about physicians' attitudes in general, and pediatricians' attitudes in particular were not previously assessed.

Aim: To assess the attitudes and beliefs of pediatricians toward transgender people, and to examine associations of demographic characteristics with these attitudes.

Methods: The transgender attitude and belief scales questionnaire (TABS) was administered to 355 pediatricians. TABS consist of three domains: interpersonal comfort, sex/gender beliefs, and human value, with respective ranges: 14-98, 10-70, and 5-35; higher scores reflect more favorable attitudes. Demographic information was analyzed.

Results: The final study cohort comprised 221 (62%) females, 132 (37%) males and 2 who defined themselves as others; 226 (63%) were senior pediatricians and 136 interns. The median scores for the three domains were: interpersonal comfort: 86; sex/gender beliefs: 57; human value: 35. Scores were significantly higher in all 3 domains for females than males, and for hospital than community pediatricians. Analyzing the results by tertiles showed less favorable attitudes among male than female, religious than secular, senior pediatricians than interns, and community than hospital pediatricians.

Conclusions: The medical community should take measures to promote positive attitudes towards transgender persons among pediatricians, to make treatment more attainable for children.

The N309K Pro-Protein Convertase Type 1 (PCSK1) Gene Mutation Causes Lack of Spontaneous Puberty and Primary Amenorrhea

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Introduction: PCSK1/3 gene mutations are known as a cause for congenital diarrhea and various endocrinopathies. Hypogonadotrophic hypogonadism and aberrant pubertal development due to pro-convertase dysfunction was not characterized yet. This study aimed to characterize the pubertal development in a family carrying the novel N309K mutation in the PCSK1 gene.

Methods and Results: We Identified 2 siblings who presented with severe congenital diarrhea followed by overweight and endocrinopathies during early childhood to have a novel homozygous N309K PCSK1 gene-mutation.

The female developed severe congenital malabsorptive diarrhea and was kept on parenteral nutrition for 5 years. L- thyroxin replacement was administered for central hypothyroidism diagnosed at 2 years of age. Poor growth rate and low GH response in stimulation tests lead to GH therapy. Severe obesity was noticed since the age of 6 years with BMI -21.6 .

Pubertal development started late at 12 years with breast developing only up to Tanner stage 2. No menarche occurred by the age of 14 years. Basal and LHRH stimulated LH levels were low. Estradiol levels were undetected.

Gradual replacement therapy with Estrogen at 14 years of age resulted in pubertal progression with secondary sexual signs, addition of progesterone achieved menarche and regular periods.

Conclusions

This case illustrates the crucial role of the prohormone convertase 1/3 PCSK in processing of LHRH, LH and FSH and enabling normal pubertal development in females. The novel homozygous N309K mutation causes severe obesity associated with hypogonadotrophic hypogonadism and primary amenorrhea that fully respond to hormonal replacement therapy.

Hyperglycemia Affects the Pituitary Gonadotropes Directly, Altering the Epigenome and Lowering FSH Levels

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The connection between metabolic state and fertility is well-recognized, and the hypothalamus clearly plays a central role in translating metabolic signals into altered GnRH release, to affect the reproductive axis. However, we hypothesized that the gonadotropes might also directly impart some of the effects of hyperglycemia on reproductive function. Gonadotropes were shown to express predominantly the insulin-independent Glut-1 transporter, and their incubation in high glucose increases expression of the glucose responsive *Txnip* gene, while levels of various glucose metabolites were altered. The drop in NAD+ and increase in α-ketoglutarate would likely alter the activity of Sirtuin histone deacetylases, JmjD histone demethylases and Tet DNA hydroxymethylases/demethylases, all of which use these metabolites as cofactors. Accordingly, gonadotropes in high glucose showed elevated histone acetylation and H3K4 trimethylation, reduced DNA methylation and increased hydroxymethylation, all of which are associated with elevated gene expression. Transcriptome analysis revealed that expression of many genes increased after incubation in high glucose. Notably however, *Fshb* expression was repressed in high glucose conditions, both in cultured cells and in two hyperglycemic mouse models *in vivo*. In one of these, circulating FSH levels were also significantly reduced. Increased expression and secretion of inhibin appears partly responsible for this repressive effect on *Fshb*. Although return of cells to normal glucose restored expression of some of the genes, *Fshb* levels remained low and the affected chromatin modifications were not reversed. Our findings suggest that hyperglycemia aberrantly affects the gonadotrope epigenome with potentially long-term effects on gene expression and thus also reproductive function.

Reproductive activity of the adult female is affected by pre-pubertal immunological stress

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Challenging environment encountered by young pre-pubertal women may affect their subsequent reproductive function, as was shown in studies on Bangladeshi women immigrants in the UK: menarche was delayed, they had lower salivary progesterone levels and early menopause than seen in the immigrants who spent their childhood in the UK. Environmental conditions might alter reproductive function through epigenetic modifications which result in altered gene expression. We aimed to find genes whose expression level changed after pre-pubertal immunological stress and elucidate its influence on the reproductive phenotype. We established a mouse model for early life immunological stress in which 23-day-old female mice were treated with DSS in their drinking water to induce temporal colitis. Puberty onset was assessed by vaginal opening and was significantly delayed by 4.9 d compared to untreated littermates. DSS treated mice also had larger litter sizes compared to controls. RNA seq analysis of the ovaries indicated 112 significantly upregulated genes and 13 significantly downregulated genes. The upregulated genes included Zdhhc21, Pkib and Akap10 which are involved in signaling pathways that regulate ovarian follicle development. One of the downregulated genes was Srd5a1 which encodes the steroid-5α-reductase which converts testosterone to dihydrotestosterone, a known factor in the regulation of ovarian follicle development; this was confirmed by RT-qPCR. These alterations in gene expression likely interfere with the regulation of ovarian follicular development and thus relate to the larger litter size of the DSS treated mice, and possibly to the early menopause of the Bangladeshi women.

Novel cyclic AMP-dependent mechanism mediates PGE2-induced FGF2 in bovine granulosa cells

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PGE2 and FGF2 are both expressed in granulosa cells (GCs) in response to LH. Thus, we examined whether PGE2 may directly stimulate FGF2 in GCs and determine its mode of action. Indeed, we found that PGE2 time-dependently elevated *FGF2*. Epiregulin (*EREG*), a known PGE2 target was stimulated as well. In support, suppressing PGE2 levels by PGH-synthase-2-silencing, reduced FGF2. PGE2 increased GCs' numbers, this effect was inhibited by FGF-receptor1 inhibitor, suggesting that FGF2 mediated PGE2 actions. Only PGE2 receptor-2 agonist (butaprost) mimicked PGE2 effects by up-regulating cAMP, *FGF2* and *EREG*. Exploring signaling pathways we observed that *FGF2* was unaffected by PKA-inhibitor (H-89) while EREG stimulated by either PGE2, butaprost or forskolin was inhibited. PKA-independent, cAMP-effector-protein: EPAC (exchange-protein-directly-activated-by-cAMP) was identified in GCs which expressed the two isoforms. Furthermore, EPAC-activator (8pCPT-AM) dose-dependently induced *FGF2* and *EREG*, while pan EPAC-inhibitor (ESI09) reduced butaprost or 8pCPT-AM induction of both genes. To specifically target EPAC isoforms, specific siRNAs were constructed. EPAC1-silencing had stronger effect on forskolin-stimulated *FGF2* and *EREG* than EPAC2-silencing. Promoter analyses of these two genes supported the results described above: Genomatix-MatInspector identified more CREB binding sites in EREG than in FGF2 (7 vs. 3) and higher number of Ras-REB (implicated in EPAC actions) in FGF2 than EREG (5 vs. 2). This study unravels novel actions of PGE2, demonstrating that FGF2 is PKA-independent but relies on EPAC1. Conversely, EREG was activated by both PKA and EPAC1 pathways. Elevated FGF2 can act as autocrine survival factor for GCs and promote endothelial cells proliferation, supporting ovarian angiogenesis.

Estrogen Suppresses Fibrosis in the Heart in Ovariectomized Mice – the Mouse Model of Human Menopause

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Introduction: Menopause is associated with increased cardiovascular morbidity and mortality. Cardiac hypertrophy is an independent risk factor for cardiovascular disease (CVD) and is more prevalent in post- compared to pre-menopausal women and age-matched men. Cardiac fibrosis precedes the development of cardiac hypertrophy under conditions of pressure overload. The mechanisms by which estrogen reduces menopause-associated CVD if administered within the first postmenopausal years are not completely understood.

Aim: To test the effect of estradiol (E2) on markers of hypertrophy, fibrosis, apoptosis and ROS detoxification in the left ventricle (LV) of ovariectomized (OVX) mice.

Methods: Three groups of 9-week-old female mice (n=10/group) were subjected to OVX or SHAM operation and were left untreated for 6 weeks. Daily 17-β-estradiol (E2) (10μg/kg) was then administered subcutaneously for 6 weeks to OVX mice. Upon sacrifice mRNA was extracted from the heart left ventricle (LV) apex. Gene expression was determined by SYBR Green based quantitative Real Time PCR and was normalized to *GAPDH.*

Results: Body weight 12 weeks post-surgery was significantly higher in OVX compared to SHAM mice (23.39 ±0.51gr vs. 21.86 ±0.63gr; *p*0.001) and was not significantly attenuated by E2 administration (23.04 ±0.83gr vs. 23.39 ±0.51gr; $p=0.994$). OVX was associated with increased *Col3α1* expression, while E2 administration reduced the expression of *FASL*, an apoptosis marker, and *Col1α1*, *Col3α1*, *TIMP1, TGFβ1, CTGF,* markers of fibrosis.

Conclusions: Estrogen suppresses the expression of fibrosis and apoptosis markers in the LV of OVX mice and is a potential additional mechanism by which it exerts its cardio-protective effects.

Hormonal Regulation of the Tet Enzymes in Developing Gonadotropes

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Tet enzymes have a central role in regulation of gene expression during development through hydroxymethylation and demethylation of methylated DNA. We have shown that Tet1 is expressed during early stages of gonadotropes differentiation and has a distinct effect on LH by repressing the expression of *Lhb*. Tet1 is highly expressed in the pituitaries of young 6 d old mice, which have a population of proliferating cells, and is dramatically down regulated during maturation. To study this regulation, we examined several hormones along the reproductive axis and found that estrogen and androgen decrease the expression of Tet1. Chromatin immunoprecipitation revealed that the receptors for estrogen (ESR1) and androgen (AR) bind upstream of the Tet1 promoter suggesting that the effects are direct. Furthermore, mRNA stability test showed that estrogen can affect Tet1 mRNA levels also by significantly decreasing its half-life. To further ascertain the effects of gonadal steroids on Tet1 *in vivo*, we examined its expression in gonadotropes of ovariectomized and castrated mice. In both sexes, the gonadotrope cell population increased in gonadectomized mice, accompanied by elevated Tet1 mRNA levels, while treatment with estradiol or DHT lowered the levels of Tet1 mRNA to these of intact adults. These results suggest that Tet1 has a role in the proliferation and differentiation of gonadotrope precursor cells and that their maturation is completed due to its repression by the gonadal steroids. Our findings thus shed further light on the role and regulation of Tet enzymes in differentiated cells.

Plenary lecture 1:

Calcium-Sensing Receptor (CaSR) Signaling Pathway Disorders

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The extracellular calcium (Ca_o^{2+})-sensing receptor (CaSR), a G-protein-coupled receptor (GPCR), regulates Ca_o^{2+} homeostasis by detecting alterations in Ca_o^{2+} concentrations and activating G-protein mediated signalling cascades, which modulate parathyroid hormone (PTH) secretion and urinary calcium excretion. Much has been learnt about the role of the CaSR in calcium homeostasis by studying human disorders. Thus, CaSR mutations resulting in loss-of-function or gain-of-function lead to familial hypocalciuric hypercalcemia (FHH), and autosomal dominant hypocalcaemia (ADH), respectively. CaSR mutations are detected in ~65% of FHH and ~70% of ADH patients, referred to as FHH1 and ADH1, respectively. Studies have revealed genetic heterogeneity and defined two additional FHH types (FHH2 and FHH3), and another type of ADH (ADH2). FHH2 and ADH2 are due to loss- and gain-of-function mutations of G-protein subunit α_{11} ($G\alpha_{11}$), respectively, and are found in 1% of FHH and ADH patients who do not have CaSR mutations. FHH3 is due to loss-of function mutations affecting adaptor protein-2 sigma subunit (AP2σ), encoded by AP2S1. AP2, a hetrotetrameric complex, is involved in clathrin-mediated endocytosis and AP2σ mutations, which all affect the Arg15 residue that interacts with the dileucine motif of cargo proteins and comprise Arg15Cys, Arg15His and Arg15Leu, result in increased CaSR cell surface expression likely due to decreased CaSR internalisation. Such AP2σ mutations are found in 20% of FHH patients who do not have CaSR or Gα11 mutations. These studies have provided new insights into CaSR signaling and trafficking, and advanced therapeutic options, such as CaSR allosteric modulators, for disorders of calcium metabolism.

Symposia 1: Genome Editing (CRISPR) / iPS

Direct Conversion Approach and iPSCs for Disease Modelling and Future Cell-Based Therapy

Yossi Buganim
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Regenerative medicine is a new field that aims to replace damaged tissues, organs or cells by transplanting healthy cells that are derived from alternative sources of cells. Embryonic stem cells have tremendous potential in this field because they are able to become all types of cells in the human body. However, various ethical problems and cell rejection by the patient`s immune system prevent their actual use.

To overcome these obstacles, Dr. Buganim`s lab works to convert adult skin cells into cells with a high clinical value, such as nerve cells, heart cells, and embryonic stem cells. These cells are referred to as "induced cells" and look and function just like their natural counterparts in the human body. By introducing a small number of proteins into skin cells, Buganim's team reprogram the genome of the skin cells which are then converted into other cells of interest. Because the skin cells are taken directly from the patient himself, issues with immune-rejection or ethics are not relevant anymore. These induced cells can be used for disease modelling, drug screening and future cell-based therapy.

Another technology that is used in the Buganim's lab is CRISPR/Cas9. Cas9 is a bacterial protein that was found to cut viral DNA using small RNA molecule that guides it to a specific locus. Today we know how to exploit this technology to correct mutations that reside within the patient's skin cells.

In this lecture I will give a background to the direct conversion and iPSC field along with the CRISPR/Cas9 technology.

Symposia 2: Brain, Cognition and Type 2 Diabetes

DNA Editing (CRISPR) in Alzheimer Disease

Dani Offen
Sackler School of Medicine, Tel Aviv University

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by global cognitive decline involving memory, orientation, judgment, and reasoning and is the most common form of dementia in the elderly. To this day, no effective treatment for AD has yet to be discovered and the research is constantly in shift to better understand this devastating disease.

Caspases, a family of cysteine proteases, are major mediators of apoptosis and inflammation. Active Caspase-6 is abundant in plaques of AD brains. In our lab, using the novel gene editing CRISPR/Cas9 method we targeted the caspase-6 gene and reduce pathology as well as ameliorate behavioral symptoms in a mouse model of AD.

More than 50% of AD patients express the ApoE4 protein; which increases the risk of prevalence for AD since it lowers the age of onset by as much as 10-20 years. Therefore, eliminating the expression of ApoE4 presents an attractive therapeutic strategy. Application of the CRISPR approach in mice astrocytes expressing the human ApoE3 or ApoE4 resulted in a significant decrease of ApoE4 protein levels (-70%) without any significant changes in ApoE3 levels. These experiments are currently being extended to the *in-vivo* level. We hope that this novel approach will lead to development of novel gene-therapy applications for AD patients.

Symposia 3: Update in Neuroendocrine Tumors and Beyond

Update in Carcinoid Syndrome

Simona Glasberg
NET Unit, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel

Neuroendocrine tumours (NETs) are rare malignancies, with an incidence of 6.9/100,000/year, occurring mainly in the gastrointestinal tract (67.5%) and the bronchopulmonary system (25.3%). NETs may secrete many secretory products (vasoactive substances), the most prominent being 5-hydroxytryptamine (5-HT, serotonin), but also tachykinins, kallikrein or prostaglandins. The liver usually inactivates these tumour products. In approximately 40% of NET patients, when hepatic spread results in hormonally active tumour products exceeding the hepatic capacity for degradation, the classical carcinoid syndrome (CS) ensues, characterized by cutaneous flushing, gut hypermotility with diarrhea, and bronchospasm with wheezing and shortness of breath. Carcinoid heart disease (CHD, Hedinger syndrome), a rare and unique manifestation, has been described in up to 60% of patients with both NETs and CS, typically inducing abnormalities of the right side of the heart. The main therapeutic aim in patients with CS is to decrease the levels of hormonal over-secretion, mainly of serotonin, which is crucial to control the symptoms, prevent the appearance/ progression/ recurrence of CHD (and related morbidity and mortality), and eventually to inhibit tumor growth. The standard treatment for CS is the administration of somatostatin analogs (SSAs), including in higher dosages, with an overall response rate of up to 60-80%. However, when the symptoms persist or the disease eventually progress (refractory CS), other treatment options are individually considered, such as serotonin synthesis inhibitor (telotristat ethyl), Peptide Receptor Radioactive Treatment (PRRT), mTOR inhibitor (everolimus), INF-α (rarely used), or locoregional therapies (TACE/SIRT), surgical debulking, etc.However, following SSAs, there is no clear data on the best treatment sequence to date.

The control of CS has a direct influence on patients' quality of life and on survival. An individualized approach within a NET multidisciplinary team (endocrinologists, oncologists, nuclear medicine specialists, cardiologists, surgeons, pathologists, etc.) is mandatory to improve our patients` outcomes.

Swinging between Genotype and Phenotype in Von Hippel-Lindau Patients – What have we learned?

Auryan Szalat
Hadassah Medical Center, Jerusalem

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant hereditary disease, clinically classified as type 1 or 2. Type 1-VHL associates renal cell carcinoma (RCC) and retinal or central nervous system hemangioblastomas. Type 2-VHL is further divided into three subtypes 2A, 2B and 2C associating pheochromocytoma (PC) with: HB, RCC and HB, or alone, respectively. Other features as pancreas neuro-endocrine tumors (PNET), and less frequent tumors or atypical lesions may also be observed. The *VHL* gene was identified in 1993, is composed of 3 exons and localized at the chormosome 3p25. It is a typical two-hits tumor suppressing gene, encoding a protein VHL (two isoforms proteins of 213 and 160 amino-acids) which is part of the E3 ubiquitin ligase family targeting substrates for proteasome degradation. The main targeted transcription factor is the Hypoxia-Inducible Factor (HIF), key regulator of genes involved in adaptation to hypoxia. Genotype-phenotype correlation studies based on clinical and genetic characteristics of thousands of families all over the world taught us many findings: most type 2-VHL mutations are missense ones, whereas most type 1-VHL mutations are deletion or nonsense frameshift mutations; the localization (codon/exon) of mutations influences age of onset of tumors (PC, PNET) and prognosis; associated deletions of other genes (Alu Elements, HSPC300) close to *VHL* gene protect from RCC and HB development. However, different genotype-phenotype correlation between ethnic groups and intrafamilial phenotypic variations suggest other factors are involved. New tools in genetic research and accumulated comprehensive data can guide evaluation, follow-up and treatment in VHL patients.

Symposia 4: Endocannabinoid Receptor in Metabolic Disease

Diabesity-Induced Renal Dysfunction: Do Cannabinoids Contribute?

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Diabetes and obesity (termed together Diabesity), with their common metabolic and pathogenic pathways, are two major risk factors for chronic kidney disease (CKD). Whereas obese patients frequently present the two main causes of end stage renal disease, diabetes and hypertension, obesity itself can cause specific renal diseases or increase the risk of progression of kidney diseases irrespective of the underlying cause. The pathogenetic pathways through which diabesity causes/worsens renal disease are not completely understood.

As the kidney is a major source of endocannabinoids (eCBs), whose levels are elevated during diabesity, and the fact that the cannabinoid-1 receptor (CB_1R) is vastly expressed in many cell types within the kidney, the possible involvement of the eCB/CB_1R system in regulating diabesity-induced kidney injury has been recently explored by our group. The results to be presented in this presentation will describe two novel cellular mechanisms by which CB_1R may trigger the development of CKD during diabetes and obesity.

Briefly, our findings indicate that diabetes-induced upregulation in the expression and membrane translocation of the facilitative glucose transporter GLUT2, localized in the renal proximal tubule cells (RPTCs) can be mitigated by peripheral blockade or genetic ablation of CB_1R in RPTCs. This effect is mediated by inducing changes in Ca^{2+} influx and PKC-β1 expression to reduce glucose reabsorption and prevent the development of CKD. In addition, we found that CB_1R in RPTCs does not contribute to the metabolic effects associated with obesity. Yet, it has a key role in the pathogenesis of obesity-induced renal complications by regulating the LKB1/AMPK/ACC signaling pathway.

Taken together, our work highlights the contribution of the renal eCB/CB_1R system in the development of diabesity-induced kidney dysfunction, inflammation and interstitial fibrosis, and further supports the pre-clinical development and clinical testing of tissue/cell-specific CB_1R antagonists for the treatment of diabesity-related CKD.

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Oral Presentations: Diabetes Mellitus

Morbidity and Mortality of Patients with Diabetes Mellitus Hospitalized for Infectious Diseases

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Objective: Examine the prognostic implications of diabetes mellitus (DM) and the importance of glycemic control during hospitalization for infectious diseases.

Methods: Historical prospectively collected data of patients hospitalized between 2011-2013.Infection-related hospitalizations were classified according to site of infection. Median follow-up was 4.5 years. Outcome measures included in-hospital and end-of-follow-up mortality.

Results: The cohort included 8,051 patients (50% female, mean age ± SD, 68±20 years) with a primary diagnosis of an infectious disease. Of these, 2,363 patients (29%) had type 2 DM. The most common infectious sites included respiratory tract (n=3,285), genitourinary tract (n=1,804), skin and soft tissue (n=934) and gastrointestinal tract (n=571). There was no difference in admission rates of patients with and without DM according to the site of infection, except for skin and soft tissue infection which were more common among patients with DM (16% vs. 10%). In-hospital mortality risk was greater in patients with DM (aOR=1.3, 95% CI = 1.1-1.7). In the entire cohort, adjusted mortality risk (aHR, 95% CI) at the end-of-follow-up was greater among patients with DM (1.2, 1.1-1.4), with increased mortality risk following hospitalization for respiratory (1.1, 1.0-1.4) and skin and soft tissue infections (1.7, 1.3-2.3). In-hospital and end-of-follow-up mortality risk were highest among patients with and without DM with median glucose 180 mg/dl during hospitalization.

Conclusions: In patients hospitalized for infectious diseases, DM is associated with increased long-term mortality risk, specifically following hospitalization for respiratory and skin and soft tissue infections. Poor glycemic control during hospitalization is associated with increased long-term mortality.

Cannabinoid-1 Receptor Regulates Mitochondrial Dynamics and Function in Renal Proximal Tubular Cells

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Introduction: Mitochondrial morphology is highly dynamic, changing rapidly in response to altered metabolic demand or cellular stress. The balance between ongoing fusion and fission events, shaping mitochondrial structure, is detrimental for maintaining mitochondrial homeostasis. Breach in this balance has been implicated with the progression of different metabolic diseases, including obesity. Endocannabinoids (eCBs) and their corresponding cannabinoid-1 receptor (CB_1R), which plays an important role in controlling energy homeostasis, are up-regulated during obesity and modulate different aspects of mitochondrial physiology.

Aim: Here, we sought to evaluate the specific role of the eCB/CB_1R system in modulating mitochondrial morphology in the metabolically active renal proximal tubular cells (RPTCs).

Results: We found that either direct activation of CB_1R or fatty acids flux, both *in vivo* and *in vitro*, resulted in excessive mitochondrial fragmentation in RPTCs. This effect was mediated, at least in part, by modulating the phosphorylation levels of the canonical fission protein dynamin-related protein 1 (Drp1) on both S637 and S616 residues. CB_1R-induced mitochondrial fission was associated with mitochondrial dysfunction, as documented by reduced oxygen consumption and ATP production, increased reactive oxygen species and cellular lactate levels, as well as a decline in mitochondrial biogenesis.

Conclusions: Taken together, these findings suggest that mitochondrial morphology can be regulated by the eCB/CB_1R system, and therefore, its activation might contribute to the organelle's dysfunction during renal tubular injury associated with lipotoxicity and other metabolic diseases.

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Metabolic Components More Prevalent Among Fragile X Premutation Women

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Background and aim: The fragile X premutation is characterized by a large CGG repeat track (55–199 repeats) in fragile X mental retardation 1 (*FMR1*) gene. Premutation alleles of the *FMR1* gene are associated with primary ovarian insufficiency (POI). Females with POI exhibit an unfavorable cardiovascular risk profile. However, data on the cardiovascular risk in women with *FMR1* premutation are scarce. We aimed to assess the prevalence of components of the metabolic syndrome among women with this premutation.

Methods: Clinical, anthropometric and laboratory data were collected from 67 women with *FMR1* premutation and compared to the general population in Israel. The metabolic components included waist circumference≥80 cm, systolic blood pressure≥130 mm Hg or diastolic blood pressure≥85 mm Hg, triglycerides(TG)≥150 mg/dL, HDL200 mg/dL and glucose≥100 mg/dL.

Results: The mean±SD age was 33.3±5.5 years and the mean±SD CGG repeats was 81.8±20.9. Compared to the general population, central obesity was 1.6-fold higher (p =0.02) and both TG and TC were six-fold higher (p0.001) among the younger women; and TC was four-fold higher (p 0.001) among the older women. The prevalence of one metabolic component was 2-fold higher than in the general population (p 0.05). No statistically significant difference was found in HDL, blood pressure or glucose levels. Neither CGG repeats nor anti-mullerian hormone correlated with metabolic risk.

Conclusions: We identify a metabolic risk among women with *FMR1* premutation. We recommend metabolic screening for all women with *FMR1* premutation, as early diagnosis of the metabolic syndrome can prevent cardiovascular comorbidities.

Leptin Antagonists as a Tool for Research and Therapy in Chronic Kidney Disease (CKD)

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Superactive mouse and human leptin antagonists (D23L/L39A/D40A/F4lA mutants) were developed in our lab and their mono-pegylation resulted in long-acting reagents suitable for *in vivo* studies. Pegylated superactive mouse leptin antagonist (PEG-SMLA) exhibited strong orexigenic effect. Cachexia is common in patients with CKD. CKD was surgically induced by 5/6 nephrectomy in C57BL/6 mice and PEG-SMLA ameliorated CKD-associated cachexia and muscle wasting. Leptin also influences immune system and contributes to deterioration of renal function in CKD. As C57BL/6 mice resist progression of CKD we established a novel model of progressive CKD in CD1 mice, using the procedure of unilateral ureteral obstruction. PEG-SMLA treatment of CD1 mice with CKD ameliorated cachexia, muscle wasting and the progressive deterioration of CKD. Muscle fibrosis is evident in the CD1 CKD mice and the upregulated pro-fibrotic genes included TGFb1, PAI-1, TGIF1, IL-1a, IL-1b, Agt, CTGF, Akt1, Smad3 and Timp3. The downregulated anti-fibrotic genes were BMP7 and IL13Ra2. PEG-SMLA attenuated the upregulated expression of TGFb1 and Agt and normalized PAI-1 and Smad3 in the skeletal muscle and renal tissue of C57BL/6 CKD mice and normalized BMR, loss of lean mass and *in vivo* muscle function. Muscle and renal fibrosis are serious complications of CKD and are associated with increased morbidity and mortality. Thus, PEG-SMLA may offer a novel therapeutic strategy for CKD-associated cachexia, muscle and renal fibrosis that will improve the survival and quality of life of CKD patients.

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Diabetic Ketoacidosis among SGLT2i-Treated Patients: Insight from a Single Medical Center Located in the Region with the Highest Diabetes Mellitus Mortality Rate in Israel

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SGLT2i drugs have been funded by the Israeli health basket since 2017 for patients with type-2-diabetes and previous cardiovascular disease, as a result of the EMPA-REG outcome studies documenting 34% reduction in all-cause mortality. In 2015 the FDA warned that SGLT2i may result in Diabetic-Ketoacidosis (DKA). The reported DKA cases were not typical because many had type-2-diabetes and their blood glucose was slightly increased.

Objective: To describe DKA cases among patients treated with SGLT2i hospitalized in the Hadera region.

Methods: The electronic files of all hospitalized patients with DKA diagnosis (codes 250.10-13) during 2015-2017 were reviewed. Patients on SGLT2i treatment were analyzed.

Results: No cases were documented in 2015, two in 2016 and nine in 2017. DKA diagnosis and treatment within the hospital was delayed in 2(18%), length of hospital stay was 5.3±1.9 days, 10 (91%) were diagnosed in the community as type-2-diabetes. Antidiabetic treatment: insulin 7(64%), metformin 7(64%), DPP-IVi 5(45%), GLP-1 agonist 3(27%) and sulfonylureas 2(18%). Mean blood glucose was 280±84. Precipitating factors: 2(18%) had infection, 1(9%) drinking alcohol, 6(86%) stopped insulin.

Four (40%) had pre-hospitalization clinical signs suggestive of LADA of these: 3 were insulin treated, and 2 had recurrent DKA. Severity score was: 2(18%)-mild, 4(36%)-moderate and 5(45%)-severe; one died. Two restarted SGLT2i treatment after hospitalization, one recurred with DKA.

Conclusion: patients with obvious insulin deficiency are being treated with SGLT2i, including some with previous DKA. Community physicians and the medical center should be aware of the a-typical presentation of DKA among patients with diabetes and SGLT2i.

The Relationship between Glucose Control & Functional Indices in Older People with Diabetes

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Diabetes may be viewed as a disease of accelerated aging as it is a risk factor for physical disability, impairment in simple and complex activities and a higher risk for falls and fractures. Data from the last several years suggests that this increased risk is due not only to recognized diabetes complications but also due to an accelerated decline in physical capacity due to lower muscle quality and a more rapid decline in muscle mass and lower extremity strength over time. Aim: To find the relationship between glucose control & functional indices. Methods: A cross-sectional study conducted at the Center for Successful Aging with Diabetes at the Sheba Medical Center. Individuals with a diagnosis of type 2 diabetes over the age of 60 were included. Functional status was assessed using tools that assess aerobic, strength and balance capacities. Medical assessment was conducted through interview, physical examination and collection of information from medical records. The association between physical indices and A1C was assessed using linear regression. Results: 159 consecutive individuals were evaluated. There was an inverse association between A1C and score achieved on the 6-minute walk; with increasing meters walked on the 6-minute walk test there was a reduction in A1C ($p=0.003$). There was also an inverse association with the 10 meter-walk ($p=0.007$), BERG balance test ($p=0.0006$), Time Up & Go ($p=0.01$). Conclusion: In this cohort of older people with diabetes there was an association between A1C and measures functional indices.

Food Restriction followed by Refeeding with a Casein- or Whey-Based Diet Differentially Affects the Gut Microbiota of Pre-Pubertal Male Rats

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Researchers are gaining an increasing understanding of host-gut microbiota interactions, but studies of the role of gut microbiota in linear growth are scarce. The aim of this study was to investigate the effect of food restriction and refeeding with different diets on gut microbiota composition in fast-growing rats. Young male Sprague Dawley rats were fed regular rat chow ad libitum (control group) or subjected to 40% food restriction for 36 days followed by continued restriction or ad libitum refeeding for 24 days. Three different diets were used for refeeding: regular vegetarian protein chow or chow in which the sole source of protein was casein or whey. In the control group, the composition of the microbiota remained stable. Food restriction for 60 days led to a significant change in the gut microbiota at the phylum level, with a reduction in the abundance of Firmicutes and an increase in Bacteroidetes and Proteobacteria. Rats refed with the vegetarian protein diet had a different microbiota composition than rats refed the casein- or whey-based diet. Similarities in the bacterial population were found between rats refed vegetarian protein or a whey-based diet and control rats, and between rats refed a casein-based diet and rats on continued restriction. There was a significant strong correlation between the gut microbiota and growth parameters: humerus length, epiphyseal growth plate height, and levels of insulin-like growth factor 1 and leptin. In conclusion, the type of protein in the diet significantly affects the gut microbiota and, thereby, may affect animal`s health.

Oral Presentations: Bone - Related Endocrine Mechanisms

The Effect of Various Phytonutrients on Bone Health in Both Human Osteoclasts and Osteoblasts Cultures

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In normal bone, there is constant construction and destruction of bone matrix called bone remodeling. Bone is reabsorbed by osteoclasts (resorption), after which new bone is deposited by osteoblasts. During osteoporosis there is excessive bone resorption and inadequate formation of new bone leading to thinning of the bone matrix. Several clinical and epidemiological studies show that some phytonutrients have beneficial effect in osteoporosis. The aim of the current study was to examine the effect of various phytonutrients on osteoblasts and osteoclasts and determine whether combinations of dietary derived compounds improve parameters of bone health. We used human primary osteoblasts and examined alkaline phosphatase (ALP) levels as a marker for osteoblasts activity. Treatment of osteoblast during osteogenic differentiation with Carnosic acid or Curcumin led to increased ALP levels. We examined mineralization by staining with Alizarin Red-S, and found increased mineralization after 3 weeks incubation with osteogenic medium. Osteoclast differentiation was measured by a quantitative assay for Tartrate Resistant Acid Phosphatase (TRAP) and by counting osteoclasts as TRAP positive multinucleated cells. Osteoclast differentiation was studied in monocytes isolated from human blood and treated with M-CSF and RANKL. Carnosic acid or Curcumin inhibit human osteoclast differentiation as measured by reduction of osteoclast counts and TRAP activity. Our findings suggest that various phytonutrients inhibit osteoclast differentiation and induce osteoblast differentiation. We posit that the outcome of our study will be useful for reducing the health burden of various types of osteoporosis.

Key words: Osteoclasts, Osteoblasts, Phytonutrients, ALP, TRAP

Catch Up Growth, What Limits It?

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Catch-up growth is defined as the periods of growth acceleration following periods of growth attenuation, bringing the child back to his/her original growth trajectory. In some cases, however, catch-up growth is incomplete, leading to a permanent growth deficit. The aim of this study was to investigate the mechanisms that limit catch-up growth. Specifically, we focused on the crosstalk between leptin, which is increased by re-feeding, and sex hormones, which increase with age. *In-vivo* studies were performed in young male Sprague Dawley rats fed *ad libitum* or subjected to 36 days of 40% food restriction followed by 90 days of re-feeding. *In-vitro* studies were performed on ATDC5 cells. Analyses of mRNA and protein levels were performed using qPCR and western blot, respectively. *In-vivo*, animals showed incomplete catch-up growth in body weight and humerus length after 90 days of re-feeding. *In-vitro* studies showed that leptin significantly increased aromatase gene expression and protein level as well as the expression of estrogen and leptin receptors in a dose- and time-dependent manner. The effect of leptin on aromatase was direct and was mediated through the MAPK-Erk, STAT3, and PI3K pathways. In conclusion, this study suggests that there is crosstalk between leptin and aromatase. When re-feeding occurs during puberty, it may lead to increased estrogen level and activity, and consequently, irreversible premature epiphyseal growth plate closure. These results contribute to our understanding of the mechanisms that limit catch-up growth and may have important implications for the development of novel treatment strategies for short stature in children.

The Impact of a Fracture Liaison Service (FLS) On 6 and 12 Months Mortality After Hip Fracture

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Background: One-year mortality is increased following an osteoporotic hip fracture. Fracture Liaison Service has been shown to increase rates of treatment for osteoporosis post fracture and do decrease mortality in the year following the index fracture.

Aim: To compare the rates of mortality following hip fracture before and after the implementation of FLS at Soroka University Medical Center (SUMC).

Methods: Patients over age 50 admitted to SUMC with hip fracture were offered investigation follow up and treatment by the FLS. Endocrine consultation and medical treatment were given either in hospital during the rehabilitation period, or at the outpatient endocrine clinics. Rates of mortality within 6 and 12 month after hip fracture were calculated for each calendar year before (2010-2013) and after (2014-2017) the implementation of FLS at SUMC.

Results: As of July 31st 2017, 1189 patients were admitted with hip fracture to SUMC, of whom 754 joined the FLS; mean age 79.2±10.12, 67% females. Of enrolled patients 507 (67%) received in-patient or outpatient endocrine consultation. Approximately 60% of patients received anti-osteoporotic medications following hip fracture. Median follow up 18.3 months (9.7;27.7). Rates of all- cause mortality at 6 months post fracture were 17.2% pre-FLS and 12.4% post FLS (p0.05) and 12 months mortality was 20.4% pre-FLS and 17% post-FLS (p=0.087) Kaplan Maier curves showed significant differences in survival between patients who received endocrine consultation compared to those who did not (HR=5.93, p0.0001).

Conclusions: The introduction of an FLS for post-hip fracture care has a beneficial effect on subsequent mortality.

Vitamin D Supplementation Attenuates Hepatic Triglycerides Accumulation in Zebrafish Nonalcoholic Fatty Liver Disease (NAFLD) Model

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Background: Vitamin D (VitD) deficiency in humans was found to be associated with features of the metabolic syndrome such as diabetes, hyperlipidemia and non-alcoholic fatty liver disease (NAFLD). We aimed to investigate VitD therapeutic potential for NAFLD in the zebrafish (*Danio rerio*).

Methods: we first examined two diet-induced NAFLD models: (1) a high caloric diet (overfeeding; OF) administered for 8 weeks and (2) a western style-diet (WSD) administered for 2 weeks. Following establishment of NAFLD, males and females from the OF group were given high caloric diet and VitD supplementation for 8 weeks. At the end of the experiment, BMI was recorded and histological analysis of the livers was done using Hematoxylin and Eosin and Oil red O stains. Following transcriptomic analysis by RNA sequencing, differentially expressed genes were validated using quantitative Real-time PCR analysis.

Results: Both diets, OF and WSD, resulted in significant hepatic fat accumulation (5.53% and 5.28%, respectively) in comparison to controls (2.46% and 0.13%, respectively) regardless of the sex. BMI values were significantly higher in the OF group in comparison to the normally fed (NF) group (by 1.33 fold) and the WSD group (by 1.34 fold). VitD therapy resulted in significant decrease of hepatic triglycerides (by 2 fold). Gene expression analysis of VitD treated zebrafish with NAFLD compared to non-treated fish revealed sex-specific mechanisms associated with lipid metabolism and biological oxidation pathways.

Conclusion: VitD may attenuate the hepatic fat accumulation induced by overfeeding and thus provide useful therapy against NAFLD progression.

Trabecular Bone Score (TBS) Contributes to Bone Disease Assessment in Diabetic Patients

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Osteoporosis in diabetic patients is now increasingly recognized as a disease complication. People with diabetes are at higher fracture risk. Poor glucose control correlates with fracture incidence. In diabetics, both bone mineral density (BMD) and FRAX under-perform as fracture risk predictors. Recently, TBS was proposed as a promising tool in evaluation of microarchitectural damage in patients with diabetes.

Aims: To assess the differences in BMD and TBS between diabetic and non-diabetic patients and examine correlations of TBS with the degree of dysglycemia and with prevalent fractures.

*equal contribution

Methods: TBS scores were retrieved by Medimaps© software from BMD database. Diagnosis of diabetes, relevant medication and HbA1c were obtained from electronic medical records. Risk factors information was extracted from self-administered questionnaires. Data analysis was performed by R-programming language.

Results: A total of 6423 BMD results were available for analysis. 1043 examinees (16.2%) had diabetes.

The diabetic patients were older (70.1±12.6vs.64.3±12.3, p0.01) and had higher BMI (29+4.6vs26.6+4.6, p0.01). BMD was significantly higher in patients with diabetes but TBS was significantly lower in an age and BMI adjusted model. HbA1c negatively correlated with TBS in women (r=-0.23, p=0.0015). TBS was lower in diabetic patients with reported fractures (1.20±0.14vs1.24±0.14,p0.001).

Conclusions: TBS is significantly lower in patients with diabetes, correlates with the degree of glucose control and prevalent fractures.

TBS should be incorporated in a clinical decision-making model for osteoporosis in diabetic patients.

*equal contribution

Synergistic upregulation of VDR signaling and enhanced differentiation-inducing effects of the 19-nor D_2 analog PRI-5202 and Nrf2 activators in acute myeloid leukemia cells.

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Acute myeloid leukemia (AML) is one of the deadliest hematological malignancies without effective treatment for most patients. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25D_3$) and its synthetic analogs are promising alternative antileukemic agents. However, calcemic toxicity of these compounds at pharmacological doses precludes their use in clinical oncology. We have previously demonstrated that the 19-*nor* vitamin D_2 analog PRI-5202 is by two orders of magnitude more potent than $1,25D_3$ as a differentiation inducer in AML cells. Here, we show that PRI-5202 is also 5 times less calcemic than $1,25D_3$ *in vivo*. Similar to $1,25D_3$, PRI-5202 synergistically cooperated with the plant polyphenolic antioxidant carnosic acid (CA), which dramatically enhanced the prodifferentiation effects of sub-nM concentrations of the analog. This was associated with a synergistic upregulation of the vitamin D receptor (VDR/RXRa), the redox-regulating transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2), and their target genes. Remarkably, similar synergistic effects were observed when $1,25D_3$ and PRI-5202 were combined with the classical Nrf2 activator *tert*-butylhydroquinone (tBHQ). Furthermore, both CA and, particularly, tBHQ induced the expression of the activator protein-1 (AP-1) family transcription factors, known as positive regulators of myeloid differentiation, and this effect was markedly potentiated by $1,25D_3$ and, especially, by PRI-5202. These data support the involvement of the Nrf2/antioxidant response element signaling pathway in the positive regulation of the prodifferentiation transcription factors VDR/RXRa and AP-1 in AML cells. We suggest that combinations of 19-*nor* vitamin D_2 analogs and Nrf2 activators may have potential for the differentiation therapy of AML.

Regulation of thioredoxin-interacting protein (TXNIP) by IGF1 signaling in Laron syndrome-derived cells

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Background: Laron syndrome (LS) is a congenital autosomal recessive disorder caused by molecular defects of the growth hormone receptor (GHR) gene, leading to congenital IGF1 deficiency. Recent epidemiological studies reported that patients with congenital IGF1 deficiency have a reduced risk of cancer development. Thioredoxin-interacting protein (TXNIP) plays an important role in redox homeostasis and glucose metabolism. In addition, TXNIP has been identified as a candidate tumor suppressor gene.

Aim: The aim of our study was to investigate the involvement of the TXNIP gene product in IGF1R signaling pathways associated with protection of LS patients from cancer.

Methods: LS patient-derived lymphoblastoid cells and prostate cancer-derived cell lines P69 and M12 were used in this study. Quantitative Real-time PCR (qRT-PCR) was carried out following hormonal treatment at different time points. Expression levels of receptors, proteins, and activation of signaling cascades were measured by Western immunoblotting.

Results: Genomic analyses conducted on lymphoblastoid cell lines revealed that TXNIP mRNA levels in LS patients were several-fold higher than in controls. In addition, qRT-PCR and Western blot revealed that IGF1 and insulin significantly downregulated TXNIP gene expression in a time-dependent manner. Furthermore, Western blot analysis revealed that stress-induced TXNIP expression was significantly downregulated by IGF1.

Conclusions: Our analyses have identified an important novel link between the TXNIP gene and the IGF1R signaling pathway, with potential implications in the clinics as a predictive or diagnostic biomarker for IGF1R-targeted therapies. Further studies will dissect the epigenetic regulation of TXNIP in LS patients.

Oral Presentations: Thyroid

High free T3 predict long survival

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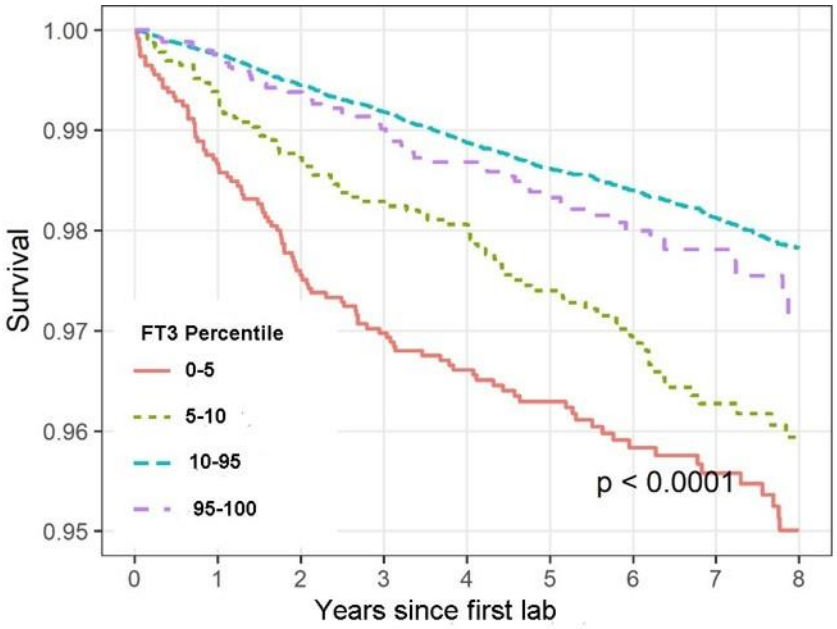

Introduction: The effect of thyroid hormones on longevity is unclear. Evaluating survival according to thyroid hormone levels in a large database may settle this issue**.**

Aim: To determine in which direction FT3 levels predict longevity.

Methods: We used a database of 95,592 FT3 measurements performed on 49,709 distinct individuals in the Jerusalem district of Clalit Health Services between 2008 and 2014. During a median follow-up of 6.9 years, 1,034 patients died. We adjusted for the influence of age and gender on FT3 levels by converting each measurement to its percentile for age and gender. We used Kaplan-Meier and multivariable Cox proportional hazard ratio(HR) models to assess survival according to ranges of initial FT3 measurement, adjusted for age and gender, we also assessed for mortality associated with FT3 variation among 16,581 individuals who underwent a second FT3 test separated by at least 1 year.

Results: Lower FT3 percentile ranges were associated with significantly increased mortality, with a HR of 3.24 (CI 2.63-4.00) for the lowest five percentiles; 1.94 (CI 1.52-2.47) for percentiles 5-10; and 1.18 (CI 1.02-1.37) for percentiles 10-50. Among patients with several FT3 measurements, mortality was increased for patients with declining FT3: HR was 2.79 (CI 1.76-4.4) for the 6.4% patients who decreased by more than 50 percentiles; 1.92 (CI 1.41-2.61) for the 18.8% who decreased between 20 and 50 percentiles; and 1.60 (CI 1.22-2.09) for the 31.5% who decreased less than 20 percentiles.

Conclusions: Lower FT3 levels as well as decline in FT3 are associated with increased mortality.

Long Term Outcomes and Prognostic Factors in Patients with Differentiated Thyroid Cancer and Bone Metastases

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Objective: Bone metastases (BM) are diagnosed in 4%-13% of patients with differentiated thyroid cancer (DTC). The objective of this study was to evaluate overall/disease-related survival of patients with DTC and BM attending a single medical center and to investigate variables predictive of better long-term outcomes.

Methods: The Rabin Medical Center Thyroid Cancer Registry was searched for patients with BM from DTC.

Results: The cohort included 63 patients (48.4% female) diagnosed at mean age 62.1±14.3 years. Primary tumor size was 41±30 mm. Most patients (63%) were stage T3/T4; 45.5% had extrathyroidal extension; 38% had lymph node metastases, 30.2% had bone-only distant metastases. Histopathology yielded papillary and follicular thyroid carcinoma in 41.3% and 31.7%, respectively, and intermediate/poorly differentiated carcinoma in 27%. Radioiodine was administered to 61/63 (96.8%) and external-beam radiotherapy in 57.8%. BM were synchronous in 67.2%. Mean follow-up was 10.5±9.7 years from detection of DTC. The common sites of BM were spine (46.9% of patients), pelvis (37.5%) and ribs (21.9%). After initial treatment 61/63 patients (96.8%) had persistent DTC. At the last follow-up, only 6 patients (9.5%) had complete remission, and structurally-progressive disease was documented in 59.7%. By the study end, 55.6% of patients had died, 39.7% of DTC. Improved survival and disease progression were associated with younger age, lower tumor stage, bone-only distant metastases, and non-spinal BM.

Conclusions: Although selected patients with DTC and BM may achieve fair long-term outcomes, novel therapies might be necessary in a significant proportion of them. The reported prognostic factors can aid in their identification.

Bone Marrow Suppression in Elderly Patients Following Empiric Radioiodine Therapy – Real-Life Data

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Background: Elderly patients with differentiated thyroid cancer (DTC) tend to have more advanced disease at presentation, for which high activities of radioiodine (RAI) is often recommended. However, the 2015 ATA guidelines recommend caution in administering activities higher than 100-150mCi in elderly patients, based on calculated bone-marrow exposure from two dosimetry-based studies.

Objectives: To evaluate real-life effect of RAI treatment on bone marrow function in elderly DTC patients. Levels of hematologic cell lines before/after RAI administration were compared.

Methods: DTC patients70 y/o who received RAI treatment and performed complete blood count (CBC) before and after treatment were included.

Results: We included 153 RAI treatments in 122 patients, 71.2% females. Mean±SD age was 75.6±4.2. Most patients had advanced disease: stage III+IV, 108 patients (72%). Median RAI activity was 150mCi (range 30-244, 65%≥150mCi) with mean cumulative activity of 183.6±131.9mCi (range 30-844). At 0-3 months there was a small but significant decrease (p0.005) in Hb (13.0±1.2 vs. 12.8±1.2), WBC (6.9±2.1 vs. 6.1±1.9),and Platelets (237±66 vs. 216±68). At 12 months follow-up there was a recovery of PLT, close to baseline. WBC and Hb values were still lower than baseline, but well within the normal range. Age, creatinine, tumor size, current dose, cumulative dose, and thyrogen use did not predict decrease within the blood lines. There were no clinically-significant cytopenia events during follow-up.

Conclusions: Empiric RAI treatment in elderly patients causes mild, clinically-insignificant bone marrow suppression. Activities higher than 100-150mCi can be safely used when clinically indicated.

High Rate of Hearing Loss among Patients with Congenital Hypothyroidism

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Background: It has been suggested that patients with congenital hypothyroidism (CH) have a high frequency of hearing impairment. However, this association has only been explored in a few studies and the results are inconclusive.

Objectives: To assess the incidence of hearing impairment among CH patients and to analyze the characteristics of the affected patients.

Methods: Audiometry was assessed prospectively in 66 patients with CH and 49 healthy patients aged 2 to 30 years. Further examination by an otolaryngologist, including otoscopy and auditory brainstem response audiometry, was performed in cases with hearing loss.

Results: Hearing impairment was found in 16 patients (24%) with CH and none in the control group. Among the hearing-impaired patients, 3 (4.5%) had sensorineural hearing loss and 13 (19.5%) had mild conductive hearing loss. Two of the patients with sensorineural hearing loss had a thyroperoxidase (TPO) mutation and one had thyroid agenesis. Among the patients with conductive hearing loss, 8 had an ectopic gland, 2 had the TPO mutation, 1 had agenesis and 2 had transient CH.

Conclusions: Our findings indicate a high rate of hearing loss, either sensorineural or conductive, in CH patients. Whether these findings relate to thyroid hypofunction, patient non-adherence or late L-T4 initiation needs to be further explored.

Diagnosing and Managing Multiple Endocrine Neoplasia type 1 (MEN1)-Related Pancreatic Neuroendocrine Tumors in Israel:

A Specialist Center Experience

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Background: MEN1 (Multiple Endocrine Neoplasia type 1), a hereditary neoplastic syndrome with an estimated frequency of ~1/30,000, is characterized mainly by the appearance of primary hyperparathyroidism, pancreatic neuroendocrine tumors (PNETs), and pituitary tumors. MEN1 patients have a decreased life expectancy, mainly related to the PNETs that are usually multifocal, larger, more aggressive and resistant to treatment.

Aim: to explore the clinico-pathological and the long-term therapeutic outcome in our MEN1-related PNETs.

Methods: Retrospective review of all consecutive MEN1 patients treated at our tertiary referral university medical centre.

Results: PNETs were diagnosed in 23/32 MEN1 patients (72%) (15 women (65%); mean age at diagnosis of 41 years (16-68); mean follow-up period of 15 years (4-37)). 19 PNETs were nonfunctioning (83%), and four were functioning (three insulinomas and one gastrinoma). 13 (56%) were multifocal (up to 18 foci), with a mean size of 1.6 cm (range 0.3-18 cm). Histopathologically, 10 PNETs (71%) were grade 1 and four PNETs (29%) were grade 2 (out of 14 patients with available reports). 15 patients (65%) were operated on; systemic therapy for progressive disease included SSAs, PRRT, everolimus & chemotherapy in 14 (61%), 5 (22%), 2 (8%) and 1 (4%) patients, respectively. 19/23 (83%) PNETs patients were alive at the end of the follow-up.

Conclusions: Our data reveals that the long-term outcomes of Israeli MEN1-PNETs patients are close to those reported in the literature to date. Increased awareness, early diagnosis and a multidisciplinary approach m/p improved the associated morbidity and mortality in these patients.

Increased Risk of Antithyroid Drug-induced Agranulocytosis with Amiodarone

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Aim: Agranulocytosisis occurs in 0.2-0.5% of patients treated with antithyroid drugs (ATD) methimazole and propylthiouracil (PTU). Our objective was to evaluate the risk for agranulocytosis, associated with ATDs, in patients with amiodarone-induced thyrotoxicosis (AIT), compared to other etiologies.

Methods: A retrospective cohort study within Clalit Health Care database was conducted of all patients with thyrotoxicosis, newly treated with ATD between 1.1.2002-31.12.2015 and followed until 3 months from the last ATD prescription dispensing, or an event of agranulocytosis.

Results: The cohort included 14,781 patients with thyrotoxicosis treated with ATDs. 39 patients (0.3% of the cohort) developed agranulocytosis during 40,551 years of follow-up: incidence rate 9.62 (6.84-13.15) for 10,000 years of follow up. Mean follow-up time was 2.7 years (SD 3.1 years). Agranulocytosis occurred after a median of 55 days.

Higher ATD dose was independently associated with higher risk for agranulocytosis HR 3.53 (1.64-7.63) regardless of amiodarone. Age was also associated with increased agranulocytosis risk in univariate Cox regression analysis with HR=1.02 (1.01-1.04) for each 1-year increase.

593 of 14,781 patients were treated with amiodarone at cohort entry. 1.3% of AIT patients developed agranulocytosis on ATD therapy, as opposed to only 0.2% of patients with thyrotoxicosis due to other etiologies. In a Cox regression multivariable model amiodarone treatment at cohort entry was associated with significantly higher risk for developing agranulocytosis during ATD treatment independently of dose and age, HR 5.15 (2.10-12.60).

Conclusion: AIT patients are at increased risk for ATD-associated agranulocytosis. Higher ATD dose is an independent risk factor for agranulocytosis.

Reassessment of Differentiated Thyroid Cancer Patients Using

the 8th TNM classification System: a comparative study

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Introduction: Considerable modifications have been introduced in the new TNM edition.

Aims: To compare DTC patients before and after restaging, by mortality, disease severity, and disease outcome.

Methods: 433 patients restaged according to 8th edition were compared to 7th edition for clinicopathological data, treatment modalities, disease outcome.

Results: Switching to 8th edition, 97.5% patients fell into stage I-II compared to 76.4% before, only 11/102 remained stage III-IV. Disease-specific mortality was recorded in 11/433 patients, 6 of whom were stage I-II upon re-staging, compared to none before (P = ns). More recurrences were seen in stages II (P = .05) and III (P = .03) by 8th edition. Stage II was most affected, with recurrence risk increasing from 29% to 76% (P = .001) and persistence from 19% to 43% (P =.01). Considering stages I-II together, recurrence risk increased from 16.7% to 28.2% (P = .01), LN metastases from 1.9% to 26.5% (P = .01), and persistence from 10% to 15% (P = ns). Out of 129 patients 45-54 year-old, 53 shifted to stage I (20 from stage II, 29 from III, and 4 from IV) and 5 to stage II (all from stage IV). Comparing this group in stage II only, TNM 8th showed more LNM (P = .001), more DM (P = .003), higher recurrence risk (P = .002) and more persistence (P = ns).

Conclusion: While TNM 8th discriminates mortality and persistence better, it may understimate disease severity, especially in 45-55 year age-group and stage II patients

Three Meals Diet vs. Six Meals Traditional Diet, Improves Glucose Variability, Weight Loss and Total Daily Insulin dose in type 2 Diabetes

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Background: Increased overall mean glucose (OMG) in obese-T2D, often require high total daily insulin dose (TDID), leading to weight gain, further increase of OMG and TDID, a vicious cycle ever-increasing TDID. High OMG, glucose variability (GV) and TDID are associated with diabetes complications. Three-meal diet-intervention with high-energy-breakfast (3Mdiet), improved OMG and weight loss (WL) in obese orally treated T2D.

Objective: To compare the effects of 12wks nutritional intervention: 3Mdiet versus 6-meals diet evenly distributed along day (6Mdiet) on WL, OMG, GV and TDID, in uncontrolled insulin treated T2D.

Methods: Twenty-nine T2D (age 69±7.2yrs, BMI:32.2±5.1kg/m^2) were randomly assigned to two isocaloric interventions (1600±200kcal): 3Mdiet or 6Mdiet. OMG and GV including Daily-Risk-for Hyperglycemia (HBGI) and Average-Daily-Risk-Range (ADRR), were assessed for 14 days by continuous glucose monitoring (CGM) at baseline and at 12wks. Insulin dose was titrated biweekly.

Results: After 12wks improvement of the following parameters demonstrated in 3Mdiet compared to 6Mdiet, respectively: **WL** (-5.0±3.2kg vs.+0.05±1kg, p0.05), **HbA1c** decreased -1.2±0.8% (8.2±1% to 7.0±0.6%) vs.-0.2±1% (7.9±0.8% to 7.7±0.6%) (p0.05). **Overall Mean Glucose** decreased in 3Mdiet by -40±23mg/dl (169±34 to129±11mg/dl) vs.-18±24mg/dl (174±44 to156±42mg/dl) in 6Mdiet (p0.05). 3Mdiet reduced **GV** indices: **HBGI** by 62%; **ADRR** by 55%, compared to 6Mdiet (P0.05). **TDID** significantly decreased in 3Mdiet vs. 6Mdiet: -20.5±24.7units/day vs. increase by 2.2 units/day in 6Mdiet (p0.05).

Conclusions: In uncontrolled insulin treated T2D, 3Mdiet was more effective vs.6Mdiet for WL, reduction of overall glycemia, HbA1c, GV and TDID. Therefore, meal timing with 3Mdiet with high-energy-breakfast should be strategy to improve diabetes control and outcome.

Optoacoustic Imaging of Blood Oxygenation in FXIII Overexpressing Murine Placentae Reveals Decreased Hemoglobin Levels in Placental Circulation.

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Introduction: ECM remodeling, regulated among others by transglutaminases (TGs), participates in proper formation and appropriate function of the placenta. Expression of Factor XIII (FXIII), a prominent TG isoenzyme has been demonstrated at the embryo-maternal interface during early implantation. We therefore aimed at exploring the possible involvement of FXIII in placental function.

Methods: Blastocysts were infected with control or FXIII over-expressing (OE) vector and then transferred into the uteri of foster mice (1). The pregnant dams at embryonic day 16.5 (E16.5) were subjected to a hyperoxia-to-hypoxia challenge. During each phase hemoglobin (Hb) and oxyhemoglobin (HbO_2) saturation data was acquired using Multispectral Optoacoustic Tomography (MSOT).

Results: Control and FXIII OE placentae were analyzed from 6 and 8 dams respectively (12 placentae). FXIII OE placentae showed significantly lower levels of Hb and HbO_2 at all oxygen levels (P0.001). Hypoxic challenge of 10% O_2 in the FXIII OE placentae showed significantly higher levels of SO_2^{MSOT} (P=0.0208).

Conclusions: OE of FXIII in the mouse placenta caused a significant reduction in the Hb and HbO_2 levels compared to the control. Hypoxic challenge in FXIII OE placentae resulted in an impaired response of the HbO_2 that fails to release the bound oxygen into the tissue. It appears that FXIII OE in the placenta affects hemoglobin and oxygen level as well as hemoglobin saturation. These changes implicate FXIII influence on placental dysfunction and impaired oxygen transport to the developing embryo.

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GnRH Induces ERK-Dependent Bleb Formation in Gonadotrope Cells, Involving Recruitment of Members of a GnRH Receptor-Associated Signalosome to the Blebs

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We have previously described a signaling complex (signalosome) associated with the GnRH receptor (GnRHR). We now report that GnRH induces bleb formation in the gonadotrope-derived LβT2 cells. The blebs appear within ~2 min at a turnover rate of ~2–3 blebs/min and last for at least 90 min. Formation of the blebs requires active ERK1/2 and RhoA–ROCK but not active c-Src. Although the following ligands stimulate ERK1/2 in LβT2 cells: EGF GnRH PMA cyclic adenosine monophosphate (cAMP), they produced little or no effect on bleb formation as compared to the robust effect of GnRH (GnRH PMA cAMP EGF), indicating that ERK1/2 is required but not sufficient for bleb formation possibly due to compartmentalization. Members of the above mentioned signalosome are recruited to the blebs, some during bleb formation (GnRHR, c-Src, ERK1/2, focal adhesion kinase, paxillin, and tubulin), and some during bleb retraction (vinculin), while F-actin decorates the blebs during retraction. Fluorescence intensity measurements for the above proteins across the cells showed higher intensity in the blebs vs. intracellular area. Moreover, GnRH induces blebs in primary cultures of rat pituitary cells and isolated mouse gonadotropes in an ERK1/2-dependent manner. The novel signalosome–bleb pathway suggests that as with the signalosome, the blebs are apparently involved in cell migration. Hence, we have extended the potential candidates which are involved in the blebs life cycle in general and for the GnRHR in particular.

Neonatal Diabetes Mellitus Caused by a Novel *GLIS3* Mutation in Twins

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Background: GLIS3 is a transcription factor involved in the development of pancreatic β-cells, the thyroid, eyes, liver and kidneys. Mutations in *GLIS3* have been recently described as a rare cause of neonatal diabetes and congenital hypothyroidism, reported in only 19 patients to date.

Case Report: Two non-identical twins were born at term, small for gestational age, to first-cousin parents. Both developed marked hyperglycemia in the first 24 hours. During their first days, they were diagnosed with primary congenital hypothyroidism, bilateral glaucoma and polycystic kidneys. IV regular insulin was started and at 2 weeks of age, they were connected to an insulin pump and continuous glucose monitoring, with marked improvement of diabetes control. L-T_4 therapy was started on the 5^{th} day of life and bilateral eye trabeculotomy was performed at 1.5 months.

The combination of neonatal diabetes with congenital hypothyroidism and glaucoma raised the diagnosis of *GLIS3* mutation. This was confirmed by molecular analysis of the *GLIS3* gene, which identified a novel homozygous nonsense mutation c.2392CT, p.Gln798Ter located in exon 9 in both twins, and the heterozygous mutation in the parents. Currently, at the age of 1 year, both twins have mild motor retardation and low weight gain. HbA1c is around 7.7% with a daily insulin dose of 0.5 unit/kg.

Conclusions: This is the first report of neonatal diabetes caused by *GLIS3* mutation in Israel. Our findings emphasize the importance of early molecular diagnosis for the management of neonatal diabetes and for genetic consultation.

The impaired inflammatory-angiogenic balance in ovaries of PCOS mice can be reversed by pigment epithelial-derived factor (PEDF)

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting 5–15% of women at reproductive age, as well as the most frequent cause of oligo-anovulation. Whereas its etiology remains elusive, hyperandrogenism, chronic inflammation and hyper-vascularization are considered hallmarks of PCOS. We have shown that PEDF, a potent ovarian anti-angiogenic and anti-inflammatory factor restores the impaired angiogenic and inflammatory balance, which governs OHSS pathogenesis. Moreover, our *in-vitro* data showed that DHT increase IL6/8 level in human granulosa cells (GC). Our objective was to evaluate the role of PEDF in the pathophysiology and treatment and PCOS *in-vivo*.

We used an PCOS mouse-model, established by prenatal exposure to high DHT level.

qPCR gene analysis of primary GC (pGC) showed that the levels of IL6 and VEGF in PCOS-induced mice were higher than in control mice (P0.05). rPEDF decreased the PCOS-induced excessive expression of IL6 and VEGF mRNA in pGC (P0.05). Though we found no change in PEDF mRNA expression in pGC, the ratios of PEDF\IL6 and PEDF\VEGF were significantly lower in PCOS compared to PCOS+rPEDF (P0.05). Vaginal opening in recombinant PEDF (rPEDF)–treated PCOS-induced mice, occurred significantly earlier than in non-treated PCOS-induced mice (P0.05).

Our data suggest an impaired angiogenic and inflammatory ovarian balance in PCOS, induced by increased levels of androgens may be restored by rPEDF treatment. Exploring the precise anti-angiogenic and anti-inflammatory mechanisms of PEDF in the ovary could reveal new therapeutic avenues for other fertility and gynecological syndromes.

Let`s Talk about It- Addressing Sexual Dysfunction in Diabetes

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Aim: Sexual dysfunction is a common complication of diabetes. Research is sparse. Many patients are unaware of the link between diabetes and sexual dysfunction, and how to treat it. This study aims to improve this gap among healthcare diabetes professionals and patients.

Methods: We validated two questionnaires regarding sexual dysfunction in diabetes, one for healthcare staff and the second for patients with diabetes. Twenty eight healthcare givers and 200 patients were evaluated by these questionnaires on the level of awareness regarding sexual dysfunction, knowledge and self-efficacy. Baseline assessment was also performed. The intervention among the healthcare teams included four very detailed workshops on sexual dysfunction in diabetes. Evaluation with questionnaires was repeated after the intervention.

Results:

Pre-intervention: Most carers agreed they are responsible for providing support on sexual dysfunction (81%). Among patients, most stated the issue was not raised by healthcare teams (54%).

Post intervention: First, regarding the patients, less subjects stated that the issue of sexuality was not raised by their caregiver (54% vs. 44%, pre vs. post-intervention, p=0.022). Similarly, less stated their needs were not addressed (55% vs. 37%, respectively, p=0.0005). However, those proportions still remained high. Second, staff questionnaires demonstrated a small, but significant, increase in awareness (p=0.042) and improved attitude (p=0.056) towards discussing sexual function. Overall, questionnaire scores of the healthcare givers increased significantly after the intervention (p0.05).

Conclusions: There is a gap between patient needs and expectations regarding support for sexual dysfunction in diabetes clinics. Our workshop narrowed the gap but further work is required.

Which Predictors Differentiate between Obese Children and Adolescents with Metabolic Complications and Those Who are Metabolically Healthy Obese (MHO)?

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Background: Childhood obesity and associated metabolic comorbidities is a global health concern. Metabolically healthy obese (MHO) may represent a subgroup of obese individuals in which excessive body fat accumulation does not lead to adverse metabolic effects.

We aimed to determine the prevalence of MHO among Israeli obese children and adolescents and to find predictors for occurrence of metabolic syndrome (MetS) and for those who are MHO.

Methods: A longitudinal cohort study was conducted in a tertiary pediatric outpatient obesity clinic. The study included 6-17.6 years old obese patients with a BMI $\geq 95^{th}$ percentile attending the clinic between 2008-2015 and at least one-year follow-up. Demographic, anthropometric, lifestyle, and cardiometabolic data were retrieved by retrospective medical record review. Participants were dichotomized as either MHO or those with MetS -partial or complete based on the number of cardiometabolic risk factors (blood pressure, serum lipids, and glucose). Multivariable logistic regression was used to determine predictors to develop MetS and those who are MHO.

Results: 230 children (median age 9.9 years) were included, of whom 42 (18.3%) were classified as MHO. Occurrence of MetS was associated with older age, higher BMI-SDS, higher Tri-ponderal mass index (TMI), and higher insulin resistance (presence of acanthosis nigricans and a higher level of HOMA-IR).

Conclusions: A higher baseline TMI and a higher increase in TMI during follow-up were the best predictors of the occurrence of Mets. Predictors that identify risk for occurrence of cardio-metabolic morbidity can inform for whom health services for managing pediatric obesity should be prioritized.

Does a First-Degree Family History of Diabetes Impact Placental Maternal and Fetal Vascular Circulation and Inflammatory Response?

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Context: Heritability of diabetes is associated with hyperinsulinemia, impaired endothelial function and inflammatory up-regulation. However, no studies have examined whether a family history of diabetes effects placental vascular circulation.

Objective: The present study was designed to investigate the impact of first-degree family history of type 2 diabetes (FHD) on placental vascular circulation and inflammatory lesions.

Design: Observational cohort study

Patients: 339 pregnant women were divided into two groups according to presence of FHD: Group 1 included 225 subjects without FHD, and group 2 included 114 subjects with FHD.

Intervention: Placental histology was performed for vascular circulation, as well as inflammatory lesions of maternal and fetal origin. Maternal and neonatal outcome parameters were collected.

Results: Maternal vascular supply (MVS) abnormalities of the placenta were significantly higher in subjects with FHD, compared to subjects without FHD (p0.005). Fetal vascular supply (FVS) abnormalities, as well as maternal and fetal inflammatory response did not differ significantly between groups. In the GLM analysis, FHD was an independent and significant predictor of MVS abnormalities and more than doubled the risk of this outcome. Gestational diabetes incidence was significantly higher in subjects with FHD (p0.0001). Significant by-group differences in gestational diabetes persisted even after adjustment for age and BMI. Although incidence of gestational hypertensive disorders was significantly higher in individuals with a family history of diabetes, after adjustment FHD did not significantly predict this outcome.

Conclusions A first-degree FHD is significantly and independently associated with an increased rate of maternal vascular perfusion abnormalities and risk of gestational diabetes.

Managing Low Testosterone in Aging Males: A Survey of Clinical Practice Patterns Among Endocrinologists and Urologists In Israel

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Introduction: It is well established that levels of testosterone in men decrease with aging. Although being an increasing public health concern, the clinical relevance of declining androgens in the aging male and the use of replacement therapy are controversial.

Aim: To document the current practices of endocrinologists and urologists in approaching aging males with low testosterone

Methods: Members of the Israel Endocrine Society and the Israel Urological association were invited to participate in a web-based survey about the diagnostic workup and treatment of a hypothetical 64 -year-old man with suspected androgen deficiency

Results: Sixteen percent of the endocrinologists and 30% of the urologists completed the survey. All responders would check the total testosterone levels as initial blood testing but only one-third of the urologists would also ask for LH FSH levels vs.74% of endocrinologists. Thirty-five percent of urologists would offer androgen therapy for a testosterone level below 12.1nmol/L, comparing with 18% of endocrinologists. For long term therapy, 87,5% of urologists will choose testosterone undecanoate (vs. 59% of endocrinologists). None of the urologists would prescribe testosterone enanthate, comparing with 14% of endocrinologists. Sixty percent of endocrinologists would not start testosterone therapy in patients with history of prostate carcinoma or moderately severe obstructive severe sleep apnea comparing with 33% of urologists.

Conclusions: There are significant differences between urologists and endocrinologists regarding the initial workup, the biochemical criteria for diagnosis, modes of treatment, as well as the attitude concerning the contra-indications of treatment of men with testosterone deficiency

Effect Of Pre-gestational Weight And Gestational Weight Gain In Women With Gestational Diabetes Controlled With Medication On Pregnancy Outcome-

Is Recommended Weight Gain Too Liberal?

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Aim: The aim of this study was to evaluate the effect of pre-gestational body mass index (BMI) and gestational weight gain (GWG) on adverse pregnancy outcomes in women with gestational diabetes (GDM) controlled with medication.

Methods: We conducted a retrospective cohort study of GDM women treated with glucose lowering agents that were followed and gave birth between 2005-2015 in the Assaf Harofeh medical center, Israel.

Results: Classification and regression tree method identified four groups according to adverse outcomes, consisting of 74 women with pre-gestational BMI below 25, 98 women with BMI 25-31, 90 women 31-39 and 18 women above 39. Respectively, the median GWG was 12 kg (8-16), 11kg (8-15), 7.5 kg (3.75-11) and 5 kg (-1.5-11.5) (p 0.001).

The risk for composite maternal and neonatal adverse outcomes was higher in the groups of BMI 25-31 (73.5%) and 31-39 (83.3%) in comparison to BMI 25 (51.4%) and 39 (55.6%), p 0.001. In the subgroup of women with pre-gestational BMI of 25, GWG of more than the median resulted in odds ratio of 2.75 (1.07-7.08, p=0.036) for adverse pregnancy outcomes compared with women who gained less than the median. When adjusted for potential confounders, the odds ratio increased to 4.8 (1.6-14.5, p=0.001).

Conclusion: Maternal obesity is related to adverse pregnancy outcomes. Moreover, GDM women with normal pre-gestational BMI who gained weight according to IOM recommendations still experienced adverse outcomes. It is possible that weight gain recommendations for this group are too liberal.

Metabolic Changes in Patients with Multiple Myeloma

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Background: Patients with multiple myeloma (MM) have a relatively high prevalence and incidence of diabetes mellitus and hypertension, both of which are part of metabolic syndrome. Whether patients with smoldering multiple myeloma (SMM) are more prone to having metabolic syndrome has not been determined.

Aims: To investigate changes in the various components of metabolic syndrome during a follow-up of patients with MM and SMM compared to individuals without MM.

Patients: A total of 153 patients (105 with MM and 48 with SMM) and 138 healthy controls were group-matched for age and sex.

Design: Retrospective cohort study. The data were collected from medical records between 2008-2015 and assessed at the time of diagnosis and after 1, 3, and 5 years of follow-up.

Results: The patients with SMM had a significantly (p0.05) higher prevalence of diabetes (25%), hypertension (60.4%) and dyslipidemia (54.2%) compared to the controls (8%, 41.3% and 31.9%, respectively). After 1 year of follow-up, the patients with SMM had a higher risk to develop dyslipidemia (odds ratio [OR] 1.9, 95% confidence interval [CI] 1.141-3.138). The patients with MM also had a higher risk to develop diabetes, hypertension and dyslipidemia during follow-up (OR 2 95%CI 1.170-6.126 for diabetes after 1 year, OR 2.8 95%CI 1.487-5.248 for hypertension after 5 years and OR 2.1 95%CI 1.377-3.267 for dyslipidemia after 1 year).

Conclusions: Patients with MM as well as those with SMM are more prone to develop metabolic syndrome compared to individuals in the general population.

Identification of ZYG11A as a Novel Metabolic Target for IGF1 Action in Endometrial Cancer Cells

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Background: Laron syndrome (LS) is a form of dwarfism caused by growth hormone receptor (GH-R) mutations, leading to congenital IGF1 deficiency. Epidemiological studies have shown that LS patients are protected from cancer. In recent genomic analyses we provided evidence that Zyg-11 family member-A (ZYG11A), a potential cell cycle regulator, is upregulated in LS patients compared to healthy controls. ZYG11A hasn't been previously linked to the IGF1 signaling pathway and its involvement in endometrial cancer is unknown.

Aim: Our aim was to assess the regulation of ZYG11A by IGF1 and insulin in endometrial cancer cells, and to explore the role of this novel protein in this malignancy.

Methods: Uterine serous papillary carcinoma cell lines (USPC1 and USPC2), with wild-type or mutant p53, respectively, were used. Quantitative Real Time PCR (qRT-PCR) was carried out following hormonal treatment at different time points. Expression levels of proteins were measured by Western immunoblotting.

Results: qRT-PCR revealed that treatment with IGF1 or insulin resulted in reduction of ZYG11A mRNA levels in USPC1 cells in a time-dependent manner, whereas USPC2 cells expressing a mutant p53 showed an upregulation of ZYG11A. Furthermore, Western blot analysis corroborated this differential regulation.

Conclusions: Our preliminary analyses have identified a potentially important link between the ZYG11A gene and the IGF1R signaling pathway. We also showed a different regulation of ZYG11A by IGF1 and insulin, due to different expression levels of p53 between the cell lines. Further studies will be carried out to assess the role of ZYG11A in cell cycle regulation.

Disease Presentation and Remission Rate in Graves` Disease Treated with Anti-Thyroid Drugs: Is Gender Really a Factor?

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Introduction: Male gender has been associated with lower rates and shorter duration of Graves` disease remission after treatment with anti-thyroid drugs (ATDs). This resulted in early consideration of radioiodine ablation and surgery in men.

Aim: To study disease presentation and outcomes of ATD treatment in males and females with Graves' disease.

Methods: Patients treated between 2010 and 2015 for Graves` disease at an endocrinology clinic in a tertiary hospital were included.

Results: Record analysis of 235 patients (64 men) showed no difference between genders in age at diagnosis (41.4±14 vs 40±15), follow up duration (6.6±7 vs 7.7±6 years), rate of co-morbid autoimmune diseases or Graves` ophthalmopathy, free T3 values, or presence of anti-TSH receptor antibodies. Smoking was more prevalent among males (31% vs. 15%, p=0.009). Free T4 levels at presentation were slightly higher among males (46.9±21.9 vs. 40.7±17.5 pmol/L, p=0.06). All males and 168 of 171 female patients were given ATDs as first line therapy for a median time of 24 and 20 months, respectively (p=0.55). Remission rates were 47% in males and 58% in females (p=0.14). Males had lower rates of adverse effects (9% vs. 18%) and discontinuation of ATD (5% vs. 16%). Disease recurrence was comparable (14% vs 20%, p=0.32), as well as requirement of second line treatment.

Conclusion: Disease presentation in male and female patients with Graves` disease is similar. Given the comparable and high rates of remission after ATD among males and females, ATDs are an attractive first line treatment in Graves' disease for both genders.

Cushing`s Syndrome: Comparison between Cushing`s Disease and Adrenal Cushing`s

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Introduction: The most common etiologies of Cushing`s syndrome (CS) are ACTH-producing pituitary adenoma (pitCS) and cortisol-secreting adrenal lesion (adrCS).

Objective: To compare the characteristics of patients with pitCS and adrCS.

Patients: The cohort included 196 patients diagnosed with CS (age 46.8±15.6 years, 76% females) in 2000-2017 in one HMO (n=132) and one tertiary medical center (n=64): 109 (55.6%) had pitCS and 74 (37.8%) had adrCS. The remainder had ectopic ACTH secretion (4.6%) or an unclear etiology (2%). Median follow-up time was 5 years.

Results: The most common reason for CS screening was weight gain in the pitCS group (53/109, 48.6%) and adrenal incidentaloma in the adrCS group (29/74, 39.2%). Compared with patients with pitCS, the adrCS group was characterized by older age at diagnosis (51.2±15.1 vs 42.2±15.1 years, p=0.001), similar severity of hypercortisoluria (median x3.2 and x3.5 above the upper normal range), higher rate of hypertension (73.2% vs 51.5%, p=0.03), and lower rate of disease persistence/recurrence postoperatively (1.3%--1 patient with bilateral adrenal findings--vs 32.3% in pitCS). Although the proportion of patients receiving glucocorticoid for 1 month postoperatively was similar (84.9% and 83.3%, respectively), the adrCS group had a longer time to recovery of adrenal function (24.7±34.1 vs 9.9±11.1 months, p=0.005).

Conclusions: The proportion of patients with adrCS in our cohort is higher than previously reported, probably because of the growing use of abdominal imaging and detection of cortisol-secreting adrenal incidentalomas. While the severity of the hypercortisoluria is similar for adrCS and pitCS, we identified differences in clinical presentation and outcomes.

Bone mineral density (BMD) in people living with HIV evalution by Quantitative UltraSonometry (QUS)- a pilot study.

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Background: Human immunodeficiency virus (HIV) infection and antiretroviral therapy are associated with bone mineral loss and poor vitamin D status in HIV-infected people. Measuring dual-energy X-ray absorptiometry is the gold standard method to evaluate the status of bone mineral density (BMD). However, it is not always readily available.

Objective: To evaluate a portable Quantitative UltraSonometry (QUS) as an alternative technique to provide information about both bone density; evaluate the bone turnover markers in HIV-infected people.

Methods: A total of 69 men (34 HIV infected men and 35 non-HIV infected men of the same age) were tested. BMD was assessed by the Achilles quantitative ultrasonometer (GE Lunar, Madison, WI) at the calcaneal heel. The HIV status was recorded for all HIV-infected patients. Calcium regulating hormones and bone turnover markers were assessed in all participants.

Results: The mean age was 47.8±7.8 and 49.1±6.00 for the HIV-infected and non-infected population respectively. The bone mineral density was reduced in HIV infected patients. The median T score was -0.65 [(-1.13)-(0.5) in the HIV infected men vs 0.3[(-0.5) - (0.9) in non-infected P=0.026. Bone turnover markers were higher in the HIV infected patients, P1NP (ng/ml) was 48.0±14.3 vs 41.1±15.2 (P=0.057) and CTX (ng/ml) was 0.41±0.18 vs 0.29±0.11 (P=0.002). We did not find an association between the traditional risk factors of reduced BMD in the HIV infected participants.

Conclusion: Young HIV infected men have lower bone mineral density measured by QUS, and higher bone turnover markers. This should be taken in to account while treating these patients.

Bilateral Medullary Thyroid Carcinoma in a 3-Year-Old Female Patient with MEN 2A Syndrome Undergoing Prophylactic Thyroidectomy: Should Current Guidelines Be Revised?

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Introduction: Multiple endocrine neoplasia (MEN) 2A is an autosomal dominant disorder that results from mutation in the *RET* proto-oncogene on chromosome 10. Almost 100% of affected patients develop medullary thyroid carcinoma (MTC). The American Thyroid Association recommends prophylactic thyroidectomy in MEN 2A pediatric patients, with the age of the recommended thyroidectomy varying according to the codon mutation present, but usually not before the age of 5 years old.

Aim: This report questions the reliability of the currently-placed guidelines and whether the age threshold for prophylactic thyroidectomy in this particular codon mutation (634) should be lowered, in parallel with an earlier evaluation of calcitonin levels in the serum.

Methods: We present a case report including the preoperative diagnosis, operative and postoperative course of a 3-year-old female patient with MEN 2A (codon 634 mutation) who underwent prophylactic thyroidectomy. The postoperative histopathologic findings will be presented and discussed.

Results: Despite the prophylactic nature of the operation, in parallel with a borderline calcitonin increase in the serum, bilateral medullary thyroid carcinoma was discovered on pathology.

Conclusion: It is likely that the current guidelines should be revised to recommend calcitonin screening and prophylactic thyroidectomy at an earlier age for MEN 2A patients with known codon 634 mutations.

Pediatric Type 1 Diabetes Mellitus Incidence and Airborne Particulate matter in Israel

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Background: The unprecedented rise in type 1 Diabetes Mellitus (T1DM) incidence in children during the last decades calls for a study of potential environmental causes. In a systematic review and meta-analysis searching for association between air pollution and diabetes 8 studies involved T2DM and only 3 involved T1DM. Another study performed in Israel showed positive correlation between glucose levels and the presence of PM2.5 and PM10 particles in the air.

Aim: To assess possible correlation of pediatric T1DM incidence rates in towns and villages in Israel and concentration of particles in the air (PM10).

Methods: A 5 years retrospective population study. Pediatric T1DM incidence rates were calculated for the period 2012-2016 for 72 municipalities with population above 5000 in Israel based on data obtained from the national T1DM registry and the Israeli Central Bureau of Statistics. Particulate matter (PM) data obtained from the Ministry of Environmental Protection. We used multiple regression analysis and GIS techniques to explore the associations

Results: Positive correlation between pediatric T1DM incidence and the presence of PM2.5 particles in the air (r=0.2137 p=0.0715) and negative correlation between pediatric T1DM incidence and the presence of PM10 particles in the air (r=-0.3217 p=0.0059).

Conclusions: The results imply that smaller air particles may contribute to the rising incidence of pediatric T1DM in Israel. Possible mechanisms include the penetration of micro particles to different body tissues, but further research is required.

Multifocality in Differentiated Thyroid Cancer (DTC) is Associated with More Severe Disease but unlikely to be an Independent Prognostic Factor

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Introduction: Controversy exists regarding the prognostic significance of multifocal extension in DTC. **Aims**: To compare baseline characteristics and response to treatment in patients with multifocal and unifocal DTC treated at a single medical center.

Methods: DTC patients with enough data for analysis were included, 172 multifocal, 280 unifocal. Medical records were reviewed for clinico-pathological data, treatment modalities and disease outcome. Mean follow-up was 9.2 and 10.5 years, respectively.

Results: Patients with multifocal disease were older (50 vs 46 yr, p=0.003), more males (27 vs 18%, p=0.04), presented more ETE (28 vs 15%, p=0.001), more LN metastases (38 vs 20%, p=0.001), higher ATA recurrence risk (39 vs 23%; p=0.001) and more advanced disease (34 vs 18% at stage 3-4; p=0.01). PTC histopathology (93 vs 88%) and tumor size (18.7 vs 20.5 mm) were similar in both groups. Though number of foci was not available, 68% multifocal cases had bilateral disease. Primary treatment included more total thyroidectomy (94.5 vs 85.5%; p=0.001), neck dissection (30 vs 20%; p=0.02) and RAI therapy (93 vs 77%; p=0.001). Overall-persistency at 1-yr (32 vs 20%; p=0.01) and structural-persistency at last visit (12 vs 5%; p=0.01) were higher in the multifocal group; however, this difference lost significance (22 vs 14% at 1-yr and 5.3 vs 2.2% at last visit, p=ns) when stage 1-2 only patients were considered (n=100 multi and 188 unifocal).

Conclusion: Ahead of the multivariate analysis (in process), these data suggest multifocality to be a surrogate of more advanced disease rather than an independent prognostic factor

Hypothyroidism and Hyperthyroidism Swings Due to Thyroid-receptor Antibodies During Three Consecutive Pregnancies

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Background: Swinging from hypothyroidism to hyperthyroidism can be related to alternations between different types of anti-tsh.Rc.Ab (TRAb). We describe a rare case of TRAb-induced thyroid dysfunction during pregnancies.

Clinical Case: A 28-year-old woman presented on the 6th week of pregnancy with newly diagnosed hypothyroidism (TSH-25mIU/L, FT4-10.7pmol/l) and thyroxine therapy was initiated. Rapidly she developed subclinical hyperthyroidism that persisted until labor despite stopping thyroxine therapy. Serology was positive for TPO-Ab and TRAb [40 (n2.5IU/L)], bioassay: TSI-658% (n 0-140) and TBAb-22.2% (n 0-20). Pregnancy follow-up was normal and an euthyroid baby girl was born. Latent hyperthyroidism persisted during the first 2 months post-partum, thereafter she developed severe hypothyroidism (TSH-196mIU/L) with reinstitution of thyroxine therapy. Five months post-partum the patient had overt hyperthyroidism while pregnancy was diagnosed (5th week). A similar course of hyperthyroidism (despite thyroxine cassation) and positive serology was seen during that pregnancy. A healthy baby boy was born with increased TSH level at 8-days that spontaneously normalized at 14-days. Again, subclinical hyperthyroidism turned to severe hypothyroidism (TSH-308mIU/l) during the post-partum period and thyroxine therapy was restarted. The 3rdpregnancy occurred 1 year later. During this pregnancy thyroxine replacement was needed throughout the whole pregnancy, TRAb was markedly elevated. Fetal follow up was normal but the newborn boy suffered from severe hypothyroidism (TSH-150mIU/L, TRAb 40IU/L) and prolonged jaundice.

Conclusion: Changes in TRAb profile during pregnancy may cause maternal, fetal and neonatal thyroid function swings and require close clinical and laboratory follow up, including antibodies evaluation (preferably by bioassay tests).

Transcriptomic profiling of bovine corpus luteum maturation

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The corpus luteum (CL) plays a key role in reproduction, by secreting progesterone, it affects cyclicity and establishment of pregnancy. Peak progesterone concentrations are attained as the CL matures at mid-cycle. To unveil novel global changes associated with CL maturation, we analyzed transcriptomes of bovine CL on days 4 and 11, representing developing vs. mature gland. Cell-specific gene expression was determined by using enriched luteal endothelial and steroidogenic cells. Our analyses revealed 681 differentially expressed genes (363 and 318 on days 4 and 11, respectively (. Enriched GO terms in early CL were cell cycle and cell replication while immune activity and lipid metabolic process were the prominent GO terms on day 11. This study revealed novel genes that were upregulated at mid-cycle: *NOTCH4* and *JAG1* showing preferential luteal endothelial cell expression. By expressing *NOTCH4* and *JAG1*, mid-cycle CL may acquire mechanisms to prevent further blood vessel sprouting and promote their maturation. Another novel luteal endothelial-specific gene which was higher on day 11, is *CD300LG*. As adhesion molecule it would enable lymphocyte transmigration to the mature CL. Most of the genes involved in de-novo cholesterol biosynthesis (e.g *HMGCS*, *HMGCR*) and uptake from plasma (*LDLR*, *APOD* and *APOE*) were upregulated in the luteal steroidogenic cells of the mature CL. This implies that cholesterol biosynthesis and utilization constitute important complementary mechanism to steroidogenesis in achieving high progesterone levels. The profound differences revealed here between CL on days 4 and 11 provide the foundation for future studies aimed at improving CL function and fertility.

Crouzon`s Syndrome and Polyglandular Autoimmune Disease

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Background: Crouzon`s Syndrome fibroblast growth factor receptor (FGFR)- related craniosynostosis characterized by facial bone deformities. We report a patient with Crouzon`s Syndrome and autoimmune endocrinopathies.

Clinical case: A 45 years old woman presented at our department with a one-year history of weakness, pre-syncope, headaches, abdominal pain and hyponatremia. Crouzon`s Syndrome was diagnosed at infancy. At age 16 she began treatment with levothyroxine because of Hashimoto disease. At age 38, primary hypogonadism was diagnosed. Due to her symptoms a Synacthen test was performed revealing hypocortisolism. A subsequent detailed endocrine evaluation revealed primary adrenal insufficiency and confirmed primary hypothyroidism and hypogonadism. Other pituitary hormones were within normal range. Normal adrenal glands were found in tomographic scan. She is currently treated with prednisolone, fluodrocortisone, and levothyroxine.

Discussion: Crouzon`s Syndrome is an autosomal dominant genetic disorder caused by gene mutation in the FGFR2. It is characterized by facial bone deformities and occasionally with hydrocephalus, intellectual and developmental disabilities. Endocrine alterations are not a common finding. The only other cases reported had growth hormone deficiency-GHD and empty sella that might be associated with the bone deformities. Polyglandular Autoimmune Disease (PGAD) is defined by the coexistence of at least two autoimmune endocrinopathies. The adult form shows a great heterogeneity with autoimmune thyroid disease, Addison disease and Type 1 Diabetes being frequent. Primary hypogonadism is seen in 4-11% of cases.

Conclusions: To the best of our knowledge, this is the first report of PGAD associated with Crouzon`s Syndrome.

Health lifestyle and obesity of adult patients with Congenital Isolated Growth Hormone Deficiency treated in childhood.

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Introduction: Treatment of patients with childhood Growth Hormone deficiency is usually terminated at the end of puberty. Follow up into adult age is rare and inconsistent.

Aim: To assess the clinical and social characteristics of adults with congenital Isolated Growth Hormone Deficiency (cIGHD) who received Growth Hormone (hGH) treatment in childhood.

Methods: Data of 39 patients with cIGHD diagnosed in our clinic were followed into adult age (mean age 30.7 ± 13.3 yrs). All were treated by hGH in childhood. Starting age was 7 ± 4.2 yrs and duration was 2-18 yrs. Out of the cohort of 39 patients, ascertained detailed data was found for 32 patients.

Results: Mean (± SD) height for the males is 160.2 ± 10.6 cm, for the females 146.4 ± 5.4 cm. Fourteen patients have high school education, 8 ended college and 2 are in special institutions. Most are employed in manual labor. All have full sexual development and 14 are married. After cessation of GH treatment and with advancing age all have progressive increase in adiposity to the degree of obesity as revealed by high skinfold thickness and missed by BMI. Twelve patients suffer from hyperlipidemia, 4 developed diabetes mellitus, and 5 have cardiovascular diseases. One patient died. None developed cancer.

Conclusion: Patients with congenital IGHD who do not receive early and regular replacement treatment are prone to lag in achieving normal height and suffer from educational and vocational handicaps. BMI is a non-reliable index in GH deficiency.

Tumor Induced Osteomalacia: An Elusive Diagnosis

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Introduction: Tumor-induced osteomalacia (TIO) is caused by tumors that secrete fibroblast growth factor 23 (FGF23). TIO is characterized by renal phosphate wasting, hypophosphatemia, low levels of 1,25-dihydroxyvitamin D, osteomalacia, and nonspecific symptoms including bone pain and musculoskeletal weakness. Locating the culprit tumor is often challenging and complete resection is curative.

Design: Case report

Case History: We report a 28-year-old man with a 5-year history of muscle weakness, arthralgia, and skeletal pain. Biochemical investigations revealed low serum phosphorus level (1.1 mg/dL) and elevated alkaline phosphatase level (287 u/l). Serum creatinine, calcium, and albumin were normal. Serum 1,25-dihydroxyvitamin D level was low (10.1pg/ml). DXA showed severe osteoporosis. ^{68}GA-DOTATATE PET/CT scan showed tracer uptake in a 2.5x1.6cm lesion located in the right popliteal fossa and revealed multiple rib and vertebrae fractures. Plasma FGF23 levels collected from right and left median cubital veins and femoral veins were 1802 pg/ml, 1816 pg/ml, 2319 pg/ml, and 1806 pg/ml, respectively (reference range: 23.2 - 95.4 pg/ml). Alfacalcidol and phosphorus supplements were initiated.

Results: The patient underwent wide resection of the tumor. Pathology showed a mesenchymal tumor, composed of spindle cells and osteoclast-like giant cell, with free margins. Blood sample drawn 14 hours after surgery showed normal plasma FGF23 level (52.67 pg/ml). Alfacalcidol and phosphorus were stopped gradually over 1 week, as serum phosphorus level was normalized.

Conclusion: TIO diagnosis is often elusive and delayed. TIO is potentially curable and should be suspected in the setting of hypophosphatemia and nonspecific symptoms, as early diagnosis can prevent long-term disabilities.

Prevalence of Diabetes Mellitus Among Children Treated with Growth Hormone in Israel

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Background: Growth hormone (GH) is a diabetogenic hormone.

Objective: To determine the standardized prevalence ratios (SPRs) of diabetes in a cohort of children treated with GH in Israel.

Methods and patients: Between the years 1988 and 2009, 2,513 children under the age of nineteen were approved for GH treatment. The patients were categorized to a low-risk category that included patients treated for isolated GH deficiency and small for gestational age and a high-risk category included patients treated for multiple pituitary hormone deficiency, chronic renal failure, Turner syndrome and Prader-Willi syndrome. This cohort was cross linked with the Israeli National Diabetes Register for 2014 and prevalent cases with diabetes were identified. The expected number of patients with diabetes was calculated for each risk category using the diabetes prevalence rates in 2014 as a reference. SPRs were calculated for the age group 10-29 years. We also performed the sensitivity analysis, excluding 4 participants who had diabetes before the GH initiation

Results: Diabetes has been identified in 23 patients. In the low risk category there was no difference in the prevalence of diabetes compared to the general population (SPR 2.05, 95% CI 0.94-3.89). In the high risk group we there was a significantly higher prevalence of diabetes (SPR 11.94, 95% CI 6.53-20.0) compared the general population.

Conclusion: GH treatment increases the prevalence of diabetes in patients at high risk to develop the disease.

Keywords: Growth hormone treatment, diabetes, prevalence, register, standardized prevalence ratio.

Transgenic *Drosophila* Lines Expressing a Constitutively Active Human LH Receptor Variant (LHR^{D578Y}) in the Gonads Exhibit a Decreased Fecundity

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The gonadotropins and their receptors are major regulators of reproduction in mammals and are absent in insects. We previously established transgenic *Drosophila* lines expressing a constitutively-active human LH receptor variant (LHR^{D578Y}) and the wild-type receptor (LHR^{wt}; inactive in the ligand absence). Ubiquitously expression of LHR^{D578Y} -but not of LHR^{wt}- resulted in pupal lethality, and targeted expression in midline cells resulted in thorax/bristles defects. Here we examined whether expressing LHR^{D578Y} in the fly gonads alter reproduction, as observed in a transgenic mice model.

The receptor was expressed in somatic cells of the gonads using the tissue specific *traffic jam*-Gal4 driver. Western blot analysis confirmed receptor expression in the ovaries. A fecundity assay indicated that expression of LHR^{D578Y} resulted in a decrease in egg laying compared to non-driven control flies carrying, but not-expressing the transgene (~40% decrease in two independent fly lines, p0.001). Egg chambers (the equivalent of follicles in mammals) at advanced stages had a normal morphology in confocal microscopy, implying that in general folliculogenesis/oogenesis were unimpaired. No significant reduction in the number of laid eggs was seen in flies expressing the LHR^{WT} or the unrelated green fluorescence protein (10% decrease compared to non-driven flies, p0.05). The decreased fecundity demonstrates a phenotype of the active receptor expressed in the fly gonads, the prime target organs of the gonadotropins in mammals. We suggest that this *Drosophila* model may serve in gaining insight into molecular mechanisms for understanding -and possibly modifying- classical and extra-gonadal activities of the gonadotropins *in vivo*.

Head Circumstances, Birth Length, and Weight of Neonates of Mothers with Hypothyroidism

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Background: The number of publications on the head circumference of neonates of hypothyroid mothers is scant and controversial. The important role of thyroid hormones on postnatal growth, neurological development and cognition has been documented both in animals and humans. As during intrauterine development, the fetal Hypothalamic-Pituitary-Thyroid Axis, is not functionally matured, and the placenta is impermeable to TSH and is largely to T3 and T4. The question to what degree the thyroid functions of the pregnant mothers affect the fetal growth remains controversial (Bachrach 1985)

Aim: To asses` brain size, birth size, birth length and weight in neonates of hypothyroid mothers. **Methods:** Data were extracted from computerized medical records of the mothers and the neonates using the BMDP and ANOVA.

Result: Our study comprising 139 neonates (82 males and 57 females) showed that female neonates had a significantly smaller head circumference than the males 34.3±1.4 vs 33.8±1.5cm (P0.047) and that neonates of both genders had a tendency to a smaller head circumference than the control population. The birth length and weight were similar.

Conclusions: This is the first report on the head circumference (i.e. brain size), birth length and weight for both genders of neonates of mothers with hypothyroidism. Our findings may indicate that some mothers with hypothyroidism receive inadequate treatment.

New Insights into the Pathogenesis and Treatment of Polycystic Ovary Syndrome - The Role of Pigment Epithelium-Derived Factor (PEDF)

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PCOS is a syndrome associated with hyperandrogenemia and insulin resistance (IR). Evidence indicates that inflammation in PCOS is a reason for the long-term metabolic complications. A group of pro-inflammatory molecules, advanced glycation end-products (AGEs), are elevated in the serum of PCOS patients and an upregulation of their receptor, RAGE, was demonstrated in their ovaries. The AGE-RAGE axis causes production of the inflammatory cytokines IL-6 and IL-8 and worsens IR. PEDF, is a glycoprotein known for its anti-angiogenic, neurotrophic, anti-inflammatory and anti-oxidative properties. It has been shown to counter AGE-mediated IR in different cells. Its level is elevated in the serum of PCOS patients. We have recently characterized PEDF in the female reproductive system and shown it to negate both angiogenic and inflammatory pathways in ovarian hyperstimulation syndrome, which is prevalent among PCOS patients undergoing IVF treatment. Our aim is to examine the role of PEDF in the metabolic aspect of PCOS. We have established an *in-vitro* model of IR in human granulosa cell-line by chronic incubation with insulin/AGEs and induced IR in an *in-vivo* mouse PCOS model by using high fat diet. In these females, glucose response in glucose-tolerance-test was significantly different from PCOS-only mice (P0.01). Under IR conditions, we demonstrated significant elevation in PEDF (P0.02) both *in-vitro* and *in-vivo*. PEDFs receptors were significantly elevated (both mRNA (P0.01) and protein (P0.05)). Furthermore, IR conditions *in-vitro*, significantly increased IL6/8 expression (P0.01). These findings suggest that PEDF plays a role in PCOS pathogenesis and may become a novel physiological treatment for PCOS.

Insulin Detemir use is associated with higher occurrence of hypoglycemia in hospitalized patients with hypoalbuminemia

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Aim: hypoalbuminemia is a risk factor for hypoglycemia. Insulin detemir is bound to albumin, and there is a common belief that it should be avoided in patients with hypoalbuminemia. We compared the effect of insulin detemir and insulin glargine on hypoglycemia occurrence across the albumin level spectrum in hospitalized patients.

Methods: Using MDClone, a new system for clinical queries on large patient databases, we retrospectively retrieved data of all adult patients hospitalized in Rambam Healthcare campus between 1/2012 and 12/2016 who were treated with either detemir or glargine and had at least one albumin blood test while hospitalized. For each patient we recorded the lowest glucose value measured around the date where his albumin was the lowest. We compared the occurrence of hypoglycemia (glucose under 70) between patients treated with the two types of insulin, taking into account additional known risk factors for hypoglycemia.

Results: A total of 4820 patients met the inclusion criteria. There was an inverse correlation between level of albumin and risk of hypoglycemia. Use of detemir was associated with higher risk for hypoglycemia, and a multivariate model demonstrated a significantly higher risk of hypoglycemia in patients with low levels of albumin that were treated with detemir. For normal range albumin levels, risk of hypoglycemia was similar between the two types of insulin.

Conclusions: Use of detemir is associated with higher risk of hypoglycemia in inpatients with low levels of albumin. It may be advisable to consider avoiding use of detemir in patients with hypoalbuminemia.

Mcm2 Expression in Adrenocortical Tumors

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Background: In adrenocortical carcinoma (ACC), Ki67 immuno-staining is not always correlated with tumor stage; therefore, search for other proliferative markers is warranted. The minichromosome maintenance protein 2 (Mcm2) is a nuclear protein involved in DNA synthesis and its expression seemed to be of special importance as a marker of adrenocortical neoplasms.

Aim: To assess whether the amount of Mcm-2 immuno-staining (Mcm-St) varies between adrenal adenoma and ACC and whether it correlates with tumor stage.

Methods: Patho-histological sections were prepared from the formalin reserved adrenal tumors, and Mcm-2-St was determined for each tumor.

Results: The adenoma group included 15 patients and the ACC group included 14 patients. WEISS score was below 3 in all tumors in the adenoma groups, and mean WEISS score was 5.6 (range 4-8) in the ACC group. In the ACC group 7% of patients were with stage 1, 42% with stage 2, 14% with stage 3 and 35% with stage 4. The amount of Mcm-2-St was significantly higher in the ACC group than in the adenoma group (P 0.001), and within the ACC group Mcm-2-St was significantly higher in tumors stage 4 (P = 0.008). Moreover, Mcm-2-St was positively correlated with WIESS score (P 0.001) and tumor size (P 0.001). No correlation was found between WEISS score and tumor stage 4 (P = 0.755).

Conclusion: The amount of Mcm-2-St was significantly higher in the ACC group compared to adenoma group and was positively correlated with ACC stage 4.

Thyroid Dysfunction in Melanoma Patients Treated with Anti PD-1 Therapy

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Introduction: Immune checkpoint inhibitors (ICIs), including anti-CTLA 4 and anti-PD-1 therapies have revolutionized the field of oncology, providing an effective treatment for hematologic and solid malignancies considered otherwise untreatable. However, ICIs have been associated with endocrine immune-related adverse events, most notably thyroid dysfunction.

Aim: (1) Determine the prevalence of thyroid dysfunction in melanoma patients treated with PD-1 inhibitors at our institution. (2) Identify risk factors for the development of anti PD-1 induced thyroid dysfunction.

Methods: We performed a retrospective review of 155 cases of metastatic melanoma, treated at our institution with anti PD-1 therapy from 2011-2017. Thyroid functions tests were analyzed at baseline and during treatment. Overt thyroid dysfunction was defined by simultaneously abnormal TSH and FT4/FT3 levels.

Results: Of the 155 patient charts reviewed, 112 were included in the final analysis due to missing data. Of these, 43.7% developed abnormal TSH levels including 16.9% overt hypothyroidism, and 8.9% overt hyperthyroidism. The median time to onset of thyroid dysfunction was 47 days. History of hypothyroidism significantly increased the risk of overt thyroid dysfunction (OR =5.5, p = 0.002), and hypothyroidism (OR=6.62, p=0.004). A higher baseline TSH was associated with increased incidence of overt thyroid dysfunction (p=0.04) and hypothyroidism (p=0.029).

Conclusion: Thyroid dysfunction following treatment with PD-1 inhibitors is common, and patients with a higher baseline TSH or history of hypothyroidism may be at increased risk. Such patients may benefit from close monitoring of their thyroid function following initiation of anti PD-1 treatment.

Differential Effects OF INSR and IGF1R on ERK and AKT Signaling Pathways in Breast Cancer Cells

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Introduction: Insulin and insulin-like growth factor-1 (IGF1) are regarded as important players in cancer biology and, particularly, breast tumors. A large body of clinical, experimental and epidemiological data supports the concept that activation of the insulin and IGF1 signaling pathways is a critical requisite for breast cancer development and progression. However, it is still unknown why insulin (INSR) and IGF1 (IGF1R) receptors, despite the fact that they share most of their downstream cytoplasmic signaling molecules, exhibit for the most part distinct, well-defined functions.

Aim: To identify the specific effect of INSR and IGF1R on ERK and AKT pathways in breast cancer cells.

Methods: MCF7-derived stable cell lines (IGF1R-KO, INSR-KO, control) were used in this study. The expression and activation of specific genes involved in insulin and IGF1 signaling was evaluated by Western blots. IGF1R promoter activity was measured by luciferase assay. Protein interaction were evaluated by co-IP assay.

Results: Western blotting analyses showed that IGF1R silencing had a major impact on nuclear ERK1/2 activation. Promoter measurements indicate that ERK2 stimulated IGF1R promoter activity in all three cell lines, although this effect was markedly reduced in IGF1R-KO and INSR-KO cells. Furthermore, co-transfection of an IGF1R, but not an INSR, expression vector reduced the ability of ERK2 to stimulate IGF1R promoter activity.

Conclusions: Our results indicate that IGF1 signaling has a critical role in nuclear ERK1/2 activation. Taken together, IGF1R promoter activity was dependent on complex interactions involving downstream mediator molecule ERK2 as well as the cognate IGF1R protein.

Adrenal insufficiency in hospitalized patients with hyponatremia

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Introduction: Hyponatremia is a common finding in hospitalized patients but its` diagnostic work-up remains a challenge. Adrenal insufficiency (AI) is a relatively rare cause of hyponatremia, yet lethal disease if untreated. The diagnosis of AI can be overlooked as clinical and laboratory features overlap with several other comorbidities. Therefore, measuring cortisol levels in cases of unexplained hyponatremia is recommended. However, there are limited data regarding the implementation of this recommendation and prevalence of AI in hyponatremic in-patients.

Aims: 1. To determine the rate of conducting an AI evaluation in hyponatremic patients admitted to non-intensive care departments during 8 years in a single medical center. 2. To determine AI diagnosis in patients with hyponatremia and the average number of admissions until reaching diagnosis.

Methods: A retrospective cohort analysis of in-patients' presenting with hyponatremia during 8 years using electronic database. AI was defined by random cortisol levels less than 200 nmol/l and/or pathological Synacthen test.

Results: The prevalence of hyponatremia was 24.6 % (51,238/208,185) of hospital admissions. Basal cortisol level was measured in 6.1% of hospital admissions with hyponatremia. AI was diagnosed in 106 cases (3.7%) and 36% of them had only mild hyponatremia. On average, AI was diagnosed after 2.0 (range 1.0-6.0) hospital admissions with hyponatremia.

Conclusions: Our data demonstrate: 1. A low rate of AI evaluation in hyponatremic in-patients 2. The diagnosis of AI is often made late only after recurrent hospital admissions. These data imply that blood cortisol should be an integral part of evaluation in hospitalized hyponatremic patients.

Circannual Variability of Thyroid Axis Function, Based Upon TSH Results from Hypothyroid Treated and Healthy Individuals Over Time

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Aim: To determine the effect of season on thyroid function in a large out-patient cohort.

Methods: 285,000 TSH results from 40,561 hypothyroid subjects between 2010 and 2012 were compared with 2,500,000 results from 911,113 healthy individuals. The two-sample t-test for independent samples was applied for testing statistical significance of the difference in the TSH values between study and control groups. All analyses were conducted using SPSS version 22, Inc., Chicago, IL.

Results: The mean (± SD) TSH value was higher in the study than in the control group (4.1±7.4 vs 2.3±2.3 mIU/L p 0.001). Within the study group the percent of tests per month above and below the reference range (%ARR and %BRR) ranged from 33.1-16.6% and 16.9- 9.1% respectively for women and 44.7-23.1% and 14.9- 6.6% respectively for men.

In the study, but not in the control group, mean monthly TSH results were significantly higher in winter (November - February) than in summer (June – September; 4.2 vs 3.8 mIU/L p0.001).

In the study, but not in the control group a circannual difference was observed in the %ARR and %BRR. The %ARR was larger and %BRR smaller in winter than in summer (23.8% vs 20.1% p0.001 and 11.0% vs 14.1% p0.001 respectively).

Conclusions: A large percentage of hypothyroid patients are sub-optimally treated. Mean TSH values of women and elderly men on thyroid replacement therapy are higher in winter than in with summer. Thyroid hormone demand is apparently increased in winter as opposed to summer.

Primary hyperparathyroidism in the elderly

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Introduction: Primary hyperparathyroidism (PHPT) is the third most common endocrinopathy. Data on PHPT in the elderly are scarce.

Objective: To characterize elderly patients with PHTP, clinically and biochemically

Patients: 216 patients (73.6% females) aged≥75 years were diagnosed and followed at a single tertiary medical center.

Results: Mean follow-up was 11.3±5.5years. Age at diagnosis was 70.9+7.2years, and at last follow-up, 82.3±5.2years. Maximal serum calcium and maximal PTH were 11.6±0.7mg/dl and 3±2.7Xupper limit of normal(UNL), respectively. Mean urinary calcium and vitamin D levels were 208±130mg/24hours and 51.9±19.1nmol/L, respectively. Osteoporosis was diagnosed in 135 patients (62.5%; 92 with fractures, 75 after PHPT diagnosis), and nephrolithiasis, in 50; 49 patients (22.7%) had neither. Thirty-six patients underwent parathyroidectomy: they were younger than the non-operated patients at diagnosis (67.4±9.5 vs 71.6±6.3years) and had higher serum and urinary calcium levels. Patients≥70years at diagnosis (n=128), compared to younger patients, had significantly lower levels of calcium (10.2±0.7 vs 10.4±0.8mg/dl,p=0.05) and PTH (1.7 vs 2.1XUNL,p=0.05) at last follow-up. In the whole cohort, serum and urinary calcium significantly (p=0.001) decreased and vitamin D level significantly increased at last visit (10.3±0.47, 172.5±116, 68.6±23, respectively) compared with levels at diagnosis (10.6±0.7, 237±148, 51.5±19, respectively). Thirty-nine patients died during follow-up: they were significantly (p=0.001) older than the remaining patients at diagnosis (75.2±6.1 vs 70.2±6.1years) and last follow up (85.3±5.9 vs 81.6±4.8 years), with no differences in laboratory variables.

Conclusions: Most elderly patients with PHPT had at least one indication for parathyroidectomy, but only 17% were operated. Serum and urinary calcium levels decreased during follow-up.

Recombinant zebrafish (*Danio rerio*) and rainbow trout (*Oncorhynchus mykiss*) recombinant growth hormones – preparation and bioactivity

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Fish growth hormones (GH) play an important role in regulating growth, metabolism, reproduction, osmoregulation and immunity, and has thus garnered attention for their application in aquaculture. Zebrafish GH (zGH) cDNA or rainbow trout GH (rtGH) cDNA was cloned into the pMon3401 vector, expressed in MON105-competent *Escherichia coli* and purified to homogeneity. SDS-PAGE analysis in the presence of reducing agents and by SEC analysis on a Superdex 75 HR 10/30 analytical column revealed that both GHs consisted of 90% monomers. Their biological activity was evidenced by their ability to interact with ovine GH receptor extracellular domain and stimulate GH receptor-mediated proliferation in FDC-P1-3B9 cells stably transfected with rabbit GH receptor. The relative affinity of zGH and rtGH, estimated by EC_{50}, was about 38-fold and 512-fold lower, respectively, than ovine GH. This is likely the reason for the low biological activity in cells with rabbit GH receptor, ~36-fold lower for zGH and ~107-fold lower for rtGH than for human GH. The low biological activity compared to mammalian GHs was not due to improper refolding, as evidenced by circular dichroism analysis, but to lower affinity. Predicting the activity of fish GHs is problematic as there is no one single optimal *in-vitro* homologous bioassay; heterologous assays may be ambiguous, and only homologous assays are suitable for measuring activity.

Bilateral Massive Adrenal Hemorrhage Causing Acute Adrenal Insufficiency in a Patient With Emergency Hypertension

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Acute massive bilateral adrenal hemorrhage is rare condition with an elusive etiology, presenting with nonspecific abdominal or flank pain, and rarely may present as adrenal crisis.

A 59-year-old male, heavy smoker, treated for hypertension and dyslipidemia, presented with progressively severe left flank pain radiating to the back

On admission he had elevated blood pressure 193/103 mmHg with no evidence of end organs damage. Physical examination revealed mild tenderness in the upper abdomen. ECG and routine blood tests were unremarkable except leukocytosis, and elevated C-Reactive Protein (CRP) (X20 of upper limit of norm). An abdomen computed tomography (CT) scan was unremarkable. During hospitalization, hemoglobin levels dropped by 5.3 g/dL, CRP continued to rise and creatinine increased from normal to 1.39 mg/dL. An enhanced CT scan, demonstrated an enlarged, hypodense left adrenal gland, consistent with adrenal hemorrhage. The patient was stabilized and discharged.

Two days later, he was admitted again with a similar right flank pain, accompanied with elevated blood pressure 220/140 mmHg. A third CT scan demonstrated bilateral adrenal hemorrhage. The day after the patient exhibited symptoms and signs consistent with acute adrenal insufficiency accompanied by new onset hyponatremia. He was treated with intravenous hydrocortisone. Laboratory evaluation established the diagnosis of primary adrenal insufficiency. Infection was ruled out and a detailed workup for hypercoagulable state or bleeding diathesis was negative. No occult malignancy was found. A CT done 3 months later showed disappearance of the adrenal hemorrhages. However, the patient remained with permanent primary adrenal insufficiency.

Differential roles of PKC isoforms (PKCs) in GnRH stimulation of MAPK phosphorylation in gonadotrope derived cells

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The role of protein kinase C (PKC) isoforms (PKCs) in GnRH-stimulated MAPK [ERK1/2, JNK1/2 and p38)
phosphorylation was examined in gonadotrope derived cells. GnRH induced a protracted activation of ERK1/2 and a slower and more transient activation of JNK1/2 and p38MAPK. Gonadotropes express
conventional PKCa and PKCbII, novel PKCd, PKCε and PKCq, and atypical PKC-i/l. The use of green fluo-
rescent protein (GFP)-PKCs constructs revealed that GnRH induced rapid translocation of PKCa and
PKCbII to the plasma membrane, followed by their redistribution to the cytosol. PKCd and PKCε localized
to the cytoplasm and Golgi, followed by the rapid redistribution by GnRH of PKCd to the perinuclear zone
and of PKCε to the plasma membrane. The use of dominant negatives for PKCs and peptide inhibitors for the receptors for activated C kinase (RACKs) has revealed differential role for PKCa, PKCbII, PKCd and PKCε
in ERK1/2, JNK1/2 and p38MAPK phosphorylation in a ligand-and cell context-dependent manner. The
paradoxical findings that PKCs activated by GnRH and PMA play a differential role in MAPKs phos-
phorylation may be explained by persistent vs. transient redistribution of selected PKCs or redistribution
of a given PKC to the perinuclear zone vs. the plasma membrane. Thus, we have identified the PKCs involved in GnRH stimulated MAPKs phosphorylation in gonadotrope derived cells. Once activated, the MAPKs will mediate the transcription of the gonadotropin subunits and GnRH receptor genes.

A comprehensive intervention for promoting successful aging amongst below the cognitive norm older people with diabetes- a feasibility study.

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Older people with diabetes have an increased risk for disability and cognitive dysfunction. The aim of this study was to test the feasibility of a multidisciplinary (psycho-cognitive rehabilitation, physical training, nutritional guidance and medical risk factor reduction) intervention amongst older people with diabetes found to have below the norm cognitive function and sub-optimal glucose control. This was a feasibility study conducted amongst individuals with diabetes with below the norm cognitive function (MoCA score of below 26) and sub-optimal glucose control (A1C=7.5%). Individuals participated in a 2 arm intervention: a medical arm: monthly meeting with a diabetes nurse educator supervised by a diabetes specialist and consulted by study psychologist in which changes in pharmacological regimen of glucose, blood pressure and lipid control were made. A multi-disciplinary intervention including: an intensive phase- group meeting which included computerized cognitive training, aerobic, balance and strength exercise and group discussion on cognitive rehabilitation strategies development and implementation with emphasis on disease management and physical activity as well as psycho-education on various disease management aspects and a monthly consolidation phase. Outcomes included change in A1C (primary), change in strength, balance and aerobic exercise capacity as well as change in quality of life.

Results. There was an improvement in quality of life and a reduction in A1C (not statistically significant). There was however a statistically significant improvement in physical indices including aerobic capacity (6 minute walk), balance (FSST) and indices assessing the risk of fall (10 meter walk, time-up and go).

Our preliminary experience with sonography-guided percutaneous ethanol injection treatment for recurrent symptomatic thyroid cysts

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Thyroid cysts are mostly benign but may be large and symptomatic. After percutaneous drainage, most (around 80 %) refill and enlarge over time. Since the late 1990s, sonography-guided percutaneous ethanol injection treatment (PEIT) has emerged as a safe and effective conservative alternative to surgical excision in cases of recurrent thyroid cysts producing esthetic complaints or compressive symptoms. In many published series the average cystic shrinkage was above 80%, and AACE/ACE/AME guidelines (2016) recommend PEIT as the first-line treatment for relapsing benign cystic lesions.

Aim: To describe our preliminary experience with PEIT in symptomatic thyroid cysts.

Methods: Three consecutive patients (25±6.1 years; 100 % women) with symptomatic benign thyroid cysts which had relapsed after drainage were included. PEIT was conducted using the established procedure. The volume of alcohol instilled was 50% of the volume drained from the cyst. Cyst diameter and volume at baseline and follow-up, and the volume of fluid removed were measured. Early and late complications were recorded.

Results: 3 patients underwent single session PEIT. Mean initial maximum cyst diameter was 3.5±1.0 cm and mean extracted liquid volume 15±11.1 ml. During the procedure all patients experienced mild pain, two experienced moderate pain in the first 72hrs and one also had fever of 38.8. No severe complications were observed. After 10±14 weeks of follow-up, cyst volume was reduced by 52±38% and all the patients were satisfied.

Conclusions: In our initial experience, PEIT was an effective, safe and well-tolerated first-line treatment of symptomatic thyroid cysts

Our Experience with rPTH (1,84) in Two Patients with Hypoparathyroidism

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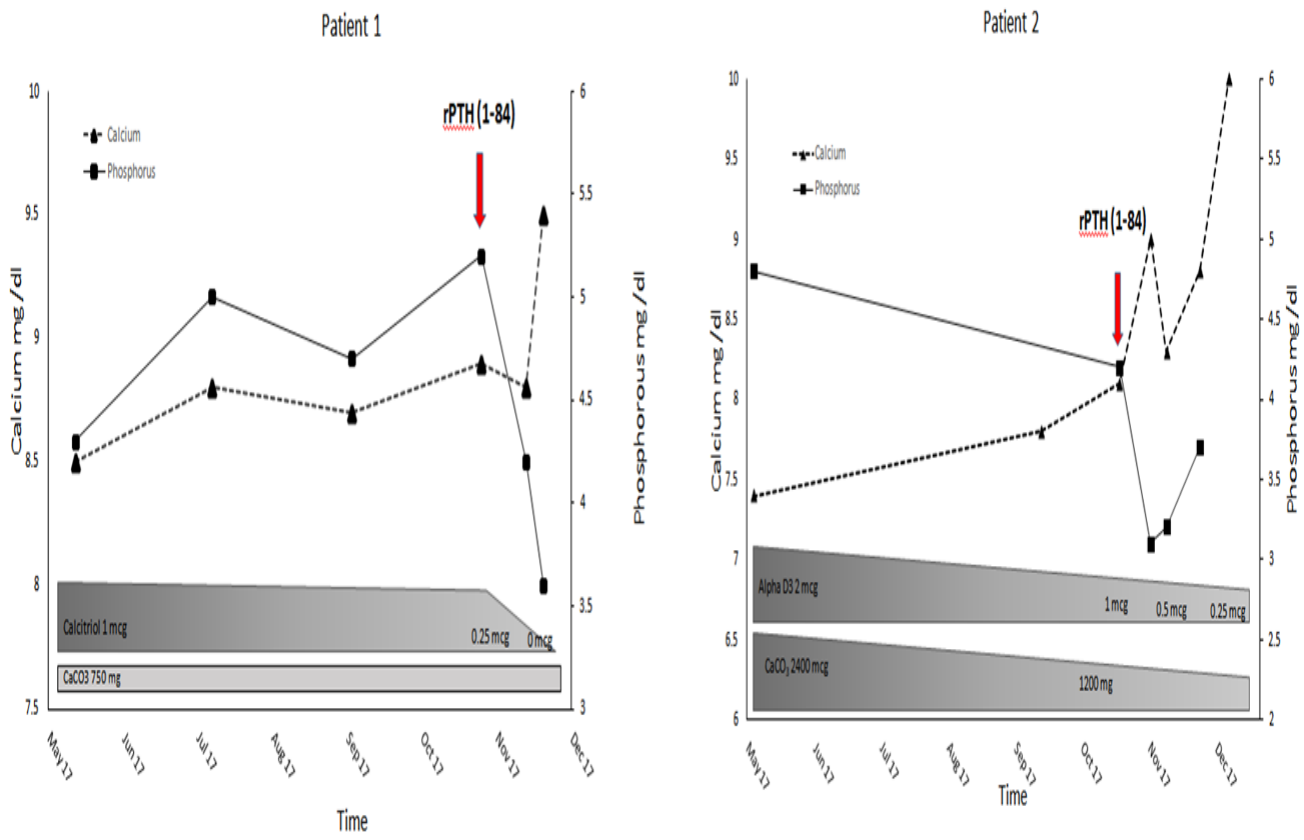
Introduction: Conventional treatment for hypoparathyroidism currently includes activated vitamin D and calcium supplements, however maintaining adequate serum calcium levels can be a challenge. Furthermore, this treatment does not fully replace the functions of PTH and can lead to both short and long-term complications. PTH replacement has recently emerged as a new treatment option.

Aim: We describe our preliminary experience with recombinant human PTH (1,84) in two patients with chronic hypoparathyroidism, ineffectively controlled with conventional therapy.

Patients/Methods: Two patients with hypoparathyroidism, inadequately controlled with conventional therapy-initiated treatment with rPTH (1,84). Serum calcium and phosphate levels were monitored weekly, as well as 24-hour urinary calcium excretion. Doses of activated vitamin D and calcium were adjusted to target serum calcium levels within the lower half of the calcium reference range.

Results: Both patients experienced significant improvement in their serum calcium and phosphate levels, along with marked decrease in their calcium and activated vitamin D requirements (figure). Both patients reported improvement in their subjective well-being. In the brief follow up period, no significant reduction in urinary calcium was noted, consistent with previous studies.

Conclusion: rPTH (1,84) is effective in improving calcium levels in patients inadequately controlled on conventional therapy. Subjects were able to significantly reduce oral calcium and active vitamin D supplements, with improvement in their overall well-being.



Impact of Support Group Sessions on Knowledge and Glycemic Control Among Patients with Type 2 Diabetes. A randomized, Placebo-Controlled Trial.

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Introduction: Diabetes self-management education (DSME) is an essential part of the lifestyle management of people with diabetes. Studies have shown that DSME have beneficial effects on diabetes knowledge, self-care behaviors and metabolic parameters. However only a minority of patients have access to such interventional programs

Aim: To evaluate the effectiveness of group education sessions in patients with type 2 diabetes mellitus

Methods: One hundred and four eligible adult patients with type 2 diabetes were studied. Fifty-four subjects were randomly assigned to interventional support program, and 55 received the usual care. The intervention program consisted of two comprehensive sessions of 4-5 hours duration each, led by a physician, a dietician and a nurse. The sessions supply a broad overview of diabetes including thorough information on nutritional and treatment aspects of the disease. Data including a questionnaire, anthropomorphic and Hba1c measurements were obtained from all participants at baseline and after 6 months

Results: The main result of the study was a significant improvement in glycemic control in the intervention participants as reflected by mean decrease of 0.24% in Hba1c at end of the trial, comparing to a decrease of 0.04% in the control subjects. (p=0.018). No significant changes in level of knowledge or in BMI or BP were showed during the study between the two groups.

Conclusions: Although the participants in the study were quite familiar with the all study materials, it seems that increased motivation and life style modifications following the education sessions lead ultimately to better glycemic control

Life Changing Decisions due to Precise Diagnosis in Families of Children with Maturity Onset Diabetes of the Young (MODY).

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Maturity Onset Diabetes of the Young (MODY) is a heterogeneous group of disorders characterized by dysfunction of beta-cells, and usually referred to monogenic forms of diabetes mellitus to distinguish them from the common types of disease such as type 1 or type 2 diabetes. *Fourteen different MODY types have been identified so far based on different gene mutations.*

Making the definite diagnosis is a challenge because of similar clinical phenotypes. Nevertheless, distinction is crucial as optimal treatments are different and the possibility of treating some of the types of MODY with oral agents.

Accurate diagnosis is significant for the proband, as well as for other members of the family. It is estimated that up to 1-2% of those diagnosed with gestational diabetes, type 1 diabetes or type 2 diabetes have MODY.

We will describe the results of molecular analyses for the currently known mutations in 11 children and their families with suspicion of MODY, the changes made in their treatment and further genetic counseling.

Influence of Ethnicity on Gestational Diabetes Mellitus in the Center of Israel: A Retrospective Cohort Study

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Aim: The aim of this study was to compare maternal and neonatal outcomes between Israeli Arab and Jewish women with GDM not controlled with lifestyle modification.

Methods: We conducted a retrospective cohort study of women with GDM who were not controlled with lifestyle modification and were followed and gave birth in a university affiliated medical center between 2005-2015.

Results: The study included 343 women, 45 (11.8%) of them Arabs. There were no differences in the baseline characteristics between the two ethnic groups including age, gravidity, parity or pre-pregnancy body mass index. There were 41.85% Jewish women with good glycemic control compared to 31.4% of the Arab women (P=0.197). A similar fraction gave birth by caesarian section or assisted labor (17.8% of the Arab versus 15.1% of the Jewish women, P=0.669). There were no differences in composite outcome comprised of pre-eclampsia, caesarian section due to diabetes, macrosomia and neonatal hypoglycemia (68.9% for the Arabs vs. 62.4% for the Jewish women p=0.42)

Conclusions: Our study did not find differences in maternal and neonatal outcomes of Arab and Jewish population of women with GDM controlled with glucose lowering agents. These results are not consistent with previous published data. It is possible that the Arab population in our study shares comparable socioeconomic elements with the Jewish one and has access to similar medical care. Other possible explanation is a small sample size of this study.

Congenital Hypothyroidism due to TSH resistance, a Spectrum of a Disease

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Background: TSH Resistance is defined as reduced thyroid sensitivity to TSH stimulation. Mostly diagnosed as Congenital hypothyroidism with elevated TSH and low T3 and T4 levels in the neonatal screen.

Methods and Results: The newborn screen of an asymptomatic male born to consanguineous parents showed TSH levels above 400 mIU/L. Thyroid replacement therapy (LT4) was initiated. Ultrasound showed residual thyroid-like tissue consistent with thyroid dysgenesis and horseshoe kidney. His aunt has adult onset Hypothyroidism.

Since age 5 years TSH levels increased over 100mIU/L inspite of adequate LT4 and normal FT4. On presentation at age 7 he showed normal growth parameter no tachycardia and good school performance indicating clinical euthyroidism inspite of consistent elevated TSH.

Family members lab tests were normal but the mother had elevated TSH with normal FT4.

Increasing the LT4 dose towards 100mcg daily resulted in partial TSH reduction with normal FT4. Clinical and laboratory course in the current and 2 other similar cases suggest TSH resistance, DNA sequencing is pending for TSH receptor and PAX-8 genes.

Conclusion: Chronically highly elevated TSH levels with normal FT4 levels despite adequate LT4 replacement suggest dysfunctional TSH receptor or its signaling pathway. The clinical euthyroidism, normal growth and intelligence suggests that elevated TSH per-se is not majorly contributing to the detrimental symptoms of hypothyroidism and should not be a critical component in prediction of the clinical outcome of such cases. In these patients Monitoring the LT4 dosing should therefore be based specifically on FT4 levels and clinical signs.

Involvement of the endocannabinoid system in the metabolic response of adipose tissue in postpartum dairy cows

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Adipose tissue (AT) plays a major role in metabolic adaptations in postpartum (PP) dairy cows. The endocannabinoid (eCB) system is a key regulator of metabolism and energy homeostasis; however, information about this system in ruminants is scarce. Previously, we showed that cows exhibiting high-weight loss (HWL) PP were insulin resistant. Here we examined the correlation between subcutaneous AT eCB `tone`, longitudinal changes in AT proteome, and the metabolic status of peripartum cows. HWL cows had higher circulating nonesterified fatty acid levels and a lower insulin/glucagon ratio PP compared with low-weight loss (LWL). Twofold elevated levels of the main eCBs, anandamide and 2-arachidonoylglycerol (2-AG), were found in AT PP compared with pre-partum HWL. AT levels of oleoylethanolamide, palmitoylethanolamide, and arachidonic acid were elevated PP compared with pre-partum in all cows. AT expressions of *CNR1* and *CNR2* tended to be higher in HWL vs. LWL PP. Proteomic analysis of AT revealed 176 differentially abundant proteins in HWL vs. LWL PP, enriching the complement and acute-phase signaling pathways. Mono-glyceride lipase was lower in HWL vs. LWL AT. Increased AT eCB `tone` coincides with greater lipolysis, AT inflammation, and insulin resistance, indicating that a metabolic syndrome exists in a subpopulation of PP dairy cows.

Hypophosphatasia: Rare metabolic bone disease with high burden of illness in adulthood

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Introduction: Hypophosphatasia (HPP) is an inherited disease of poor bone mineralization because loss-of-function mutation in the alkaline phosphatase (ALP) gene, encoding the tissue-nonspecific isoenzyme of ALP (TNSALP). The biochemical hallmark is low ALP serum level with bone and dental abnormalities. The adult form is easily missed and frequently mistreated with bisphosphonates for presumed osteoporosis, which may be detrimental.

Aims: We report 4 families presumably affected.

Methods: review of charts.

Results: Case 1: A 69 yo male with low BMD, early age fragility fractures (EAFF) and very low ALP. His mother and daughter have low ALP, the mother osteoporosis too. His brother EAFFx5 and early age dental problems (EADP), Case 2: A 70 yo female with osteoporosis, multiple EAFF (ribs age 15, knee age 30, ribs age 38, hip age 68), EADP, early age nephrolithiasis, and low ALP. Two sisters with EADP and EAFF; a daughter with EADP, low BMD and low ALP; a son with EADP and multiple EAFF. Case 3: A 80 yo female with EADP, osteoporosis, multiple EAFF, and low ALP. Her sister EADP, 4 children with low and very low ALP (2 with EADP) and a grand-daughter low ALP too. Case 4: A 81 yo female with EADP, osteoporosis, multiple EAFF, and low ALP. Her son with early age nephrolithiasis and her daughter EADP and bone pain.

Conclusion: Adult HPP presents a wide clinical spectrum, appears to be underdiagnosed and is frequently mistreated as osteoporosis. New enzyme replacement therapy (Asfotase Alfa) may be indicated in some cases.

Cyclosporine A induces Endothelin-Converting Enzyme (ECE)-1: Studies *in-vivo* and *in-vitro*

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AIM: Cyclosporine A (CsA) induces renal vasoconstriction and hypoxia and enhances the expression of endothelin-1 (ET-1) pro-hormone (pre-pro ET-1), plausibly leading to a feed-forward loop of renal vasoconstriction, hypoxia, and enhanced synthesis of the potent vasoconstrictor ET-1. Endothelin converting enzyme (ECE)-1 cleaves big endothelin to generate endothelin (ET)-1 and is up-regulated by hypoxia via hypoxia-inducible factor (HIF). We hypothesized that in addition to the direct induction of ET-1 synthesis, CsA might also intensify renal ECE-1expression, thus contributing to enhanced ET-1 synthesis following CsA.

METHODS: CsA was administered to Sprague Dawley rats (120 mg/kg/SC) for 4 days and renal HIF and ECE-1 expression were assessed with western blots and immunostaining. Human umbilical vein endothelial cells (HUVEC) and proximal tubular cell line (HK-2) were subjected to CsA and ECE-1 induction was evaluated using real-time mRNA PCR and western blots.

RESULTS: CsA intensified renal parenchymal ECE-1 expression in the rat kidney, particularly in distal nephron segments, along with renal hypoxia (detected by pimonidazole adducts) and HIF expression, in line with our recent observations showing episodic hypoxia in mice subjected to CsA. Furthermore, in cultured normoxic HUVEC and HK-2 cells, CsA dose-dependently induced both pre-pro-ET-1 and ECE-1 mRNA and protein expression, with enhanced ET-1generation.

CONCLUSIONS: CsA induces ECE-1 via both hypoxic and non-hypoxic pathways. ECE-1 may contribute to increased renal ET-1 generation following CsA, participating in a feed-forward loop of renal parenchymal hypoxia and ET synthesis.

Short term adherence with discharge recommendation for insulin treatment among patients with type 2 diabetes

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Background: Basal-Bolus (BB) insulin treatment is increasingly used in uncontrolled diabetes patients during hospitalization and is commonly recommended on their discharge. However, the extent of adherence with this recommendation is unknown.

Aim: to determine the short-term adherence of type 2 diabetes mellitus (T2DM) patients discharged from internal medicine wards with recommendation for BB insulin treatment.

Methods: Prescription (primary-physician adherence) and purchase (patient-adherence) of long acting and short acting insulins during the 1st month following discharge from internal medicine wards was determined in 336 T2DM patients. Adherence was defined as "full" if prescription/purchase of both basal (long acting) and bolus (short acting) insulin was made and as "partial" if only one kind of insulin was prescribed/purchased. Association between demographic and clinical parameters and adherence was determined.

Results: Primary-physicians' full adherence with discharge instructions was higher than patients' full adherence)76% vs. 62.2% respectively, p=0.01). Pre-hospitalization HbA1c was significantly associated with both patient`s and physicians` adherence (9.0%±2.1% in the full adherence group and 7.7%±1.3% in the no adherence group, p0.01). Age was negatively associated with adherence of primary-physicians

(73±11.2 years in the full adherence group and 65.4±15.5 years in the no adherence group, p0.01). A negative correlation between patients and physicians` adherence and Length of hospitalization was found. When the sole cause of admission was diabetes, close to 100% adherence of both primary-physicians and patients was found.

Conclusion: Short term adherence with discharge recommendation for BB insulin treatment is associated with pre-hospitalization patient characteristics and length of hospitalization

Incidence of Glucocorticoid Induced Hyperglycemia among Hospitalized Nondiabetic Patients

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Introduction: High-dose glucocorticoid therapy is a recognized cause of hyperglycemia. Given the paucity of literature regarding the incidence of glucocorticoid-induced hyperglycemia among nondiabetic patients, we commenced this study in order to assess its incidence and to identify risk factors.

Design: A retrospective longitudinal study.

Methods: We retrieved patients over 18 years old, without prior diabetes diagnosis or treatment hospitalized in Rambam Hospital between 1.1.2012 – 31.3.2017, who received ≥10 mg oral prednisone or equivalent intravenous hydrocortisone or intravenous dexamethasone, for at least 2 days. Demographic and lab values of patients who developed hyperglycemia (defined by ≥1 capillary blood glucose ≥180 mg/dl during the first 4 days of glucocorticoid treatment) were compared to those of patients who did not develop hyperglycemia.

Results: There were 671 patients who filled the inclusion criteria: 355 received oral prednisone, 164 received intravenous dexamethasone, and 152 received intravenous hydrocortisone. Incidence of glucocorticoid-induced hyperglycemia among all patients was 22.6%. Patients who developed glucocorticoid-induced hyperglycemia were older and had a higher creatinine, BUN and WBC count. Using multivariate regression analysis, age over 80 years (OR: 6.27, 95% CI 3.02-13.05), hospitalization in non-surgical wards (OR: 3.08, 95% CI 1.64-5.81), and a 4-day cumulative prednisone dose 240 mg (OR: 1.78, 95% CI 1.2-2.64), were identified as independent risk factors for hyperglycemia.

Conclusion: Older patients without prior diabetes receiving high doses of glucocorticoids should be monitored closely for the development of glucocorticoid-induced hyperglycemia. Special attention should be paid to patients receiving over 60mg prednisone/day and patients hospitalized in non-surgical departments.

Prevalence of Unexplained Anemia and Associated Clinical Parameters in Diabetes and Pre-Diabetes

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Aim: The prevalence of unexplained anemia in diabetes mellitus (DM) is not well defined. Data regarding anemia in pre-DM is extremely limited. The aim of this study was to determine the prevalence of unexplained anemia in DM and pre-DM, to define the hematologic characteristics of the anemia, and to assess association with clinical parameters.

Methods: Patients with DM and pre-DM were identified. Patients with any possible cause of anemia including eGFR

Results: Analysis of 511 patients with DM and pre-DM was conducted. The prevalence of unexplained anemia was 17.4% (61/349) in DM and 9.8% (16/162) in pre-DM. The DM anemic subjects were older (64.3±11.0 vs. 68.3±11.3, p=0.012) and had higher albumin/creatinine ratio (141.23±274.4 vs. 53.56±108.8, p=0.002). The anemic DM patients had lower iron levels (56.2 ±20 µg/dL vs. 75.1±24.3 µg/dL, p=0.001) and higher CRP levels (1.17±1.14 mg/L vs. 0.58±0.49mg/L, p0.001). In the pre-DM group, anemia was associated with higher CRP levels (1.52±1.63 mg/L vs 0.28±0.29mg/L, p0.001). Erythropoietin levels were higher in the DM anemic patients (14±3.0 IU/L vs. 9.5±5.1 IU/L, p=0.019) and hepcidin levels lower (14.8±9.1 ng/ml vs. 39±31.4 ng/ml, p=0.047)

Conclusions: In this cohort, the prevalence of unexplained anemia was significant, although lower than that reported by other studies, probably because of strict definition of unexplained anemia. Anemia was associated with albuminuria even with normal eGFR. We demonstrated that unexplained anemia is common in DM and pre-DM and may be related to aberrant erythropoiesis- related iron utilization.

High Fracture Susceptibility with Increased Frequency of Hip Fractures in Patients with Hypoparathyroidism

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Aim: The association between hypoparathyroidism (hypoPT), osteoporosis, and fracture susceptibility has not been investigated. The aim of this study was to assess the prevalence of osteoporosis and fractures in patients with hypoPT.

Methods: The computerized datacenter of the Endocrine Institute of Rabin Medical Center (1974-2017) was searched for all patients with permanent hypoPT who were also diagnosed with osteoporosis. Data on clinical and biochemical characteristics, treatment, and bone mineral density (BMD) were collected from the medical records**.**

Results: Of 104 patients with hypoPT, 18 (17.3%) had osteoporosis. All but one were postmenopausal women. The most common cause of hypoPT was surgical (thyroid cancer, 16; toxic goiter, 1). Osteoporosis was diagnosed by densitometry or fragility fractures history. Median follow-up time was 14.5 years (range 3-41). The diagnosis of osteoporosis preceded the detection of hypoPT in 7 patients (group 1) and succeeded it in 11 (group 2). Patients in group 1 were younger (53±5.9 vs. 65±9.9 years, p0.001). A total of 12 fractures were detected in 10 patients. 9 (83%) of them were in group 2 (3 hip and 3 multiple fractures) while a BMD (t-score) was in the osteoporotic range in only 7 (63.3%). Treatment consisted of teriparatide (1 patient, group 1; 3 patients, group 2), raloxifene (3 patients and 2 patients, respectively), and bisphosphonates (6 patients in each group).

Conclusions: The study suggests that hypoPT is associated with skeletal fragility and an increased frequency of hip fractures.

Effect of short-term intervention by an interdisciplinary team of diabetes specialists on glycemic control in patients with uncompensated diabetes (HbA1C ≥9%) in a community setting

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Aim Patients with uncompensated diabetes are characterized by low compliance with treatment and failure to seek timely consultation with medical experts. The aim of the study was to determine if providing access to short-term intervention by diabetes specialists in a community setting can benefit patients with uncompensated diabetes.

Methods The electronic database of 7 primary clinics of a large health management organization was searched for all patients aged 18 years with uncompensated diabetes (HbA1C 9%). The eligible patients were actively approached with an offer to attend an ambulatory interdisciplinary diabetes clinic. After 9 months, we compared HbA1C levels between those who participated in the program and those who did not.

Results Of the 504 patients contacted, 225 (45%) agreed to attend the specialized diabetes clinic (intervention group) and 227 declined (control group). Mean baseline HbA1C level was similar in the two groups (10.4%). After a median of 5 months' follow-up (range 3-9 months), the intervention group showed a significantly greater reduction in HbA1C level than the control group (-1.5% vs. -0.8%, p0.01). An HbA1C level of 9% was achieved by 55% of the intervention group compared to 37% of the control group (p0.05). Significantly more patients in the intervention group received injectable medications (insulin and GLP1 agonists; p0.05).

Conclusions Short-term intervention by an interdisciplinary team of diabetes specialists appears to improve glycemic outcome in ambulatory patients with uncompensated diabetes compared to patients without access to specialized consultation. Central computerized tracking systems can be used to identify candidates for intervention

The Effect of CAG Repeats Length on Differences in Hirsutism Among Healthy Israeli Women of Different Ethnicities

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Purpose: Variations in the degree of hirsutism among women of different ethnic backgrounds may stem from multiple etiologies. Shorter length of the polymorphic CAG repeats of the *androgen receptor* (*AR*) gene may be associated with increased activity of the receptor leading to hirsutism. We hypothesized that there are ethnic differences in the degree of hirsutism among Israeli women, and that the CAG repeats length contribute to these differences.

Methods: Healthy Israeli Jewish women aged 18-45 years of Ashkenazi and non-Ashkenazi origin were invited to participate. Hirsutism was assessed using the simplified Ferriman–Gallwey score, and serum total testosterone levels were measured. The CAG repeats length was determined by PCR.

Results: One-hundred and eight women were recruited (49 Ashkenazi and 59 non-Ashkenazi). The Ashkenazi women had a significantly lower degree of hirsutism (*P*0.01), lower mean BMI (*P*=0.003), total testosterone levels (*P*=0.017), and longer weighted bi-allelic CAG repeats mean (*P*=0.015) compared to non-Ashkenazi women. For the group as a whole, there was a significant negative correlation between the number of CAG repeats in the *AR* gene and the sFG score, while the number of repeats was not related to testosterone levels. Stepwise logistic regression revealed that ethnic origin and the CAG repeats length were the strongest factors affecting hirsutism (*P*0.001, *P*=0.03, respectively).

Conclusions: There is a significant difference in the degree of hirsutism between Ashkenazi and non-Ashkenazi women in Israel that is partially explained by CAG repeats length.

Metastatic Papillary Thyroid Carcinoma Resembling Spinal Ependymoma

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A 71-year-old female was evaluated for severe low back pain. An MRI scan demonstrated an oval, lumbar, intrathecal, 16X15 mm mass, isointense in T1, with homogeneous enhancement following Gadolinium injection, interpreted as consistent with a "spinal ependymoma". Accordantly, the patient was scheduled for spinal surgery.

During pre-operative evaluation a huge multinodular thyroid goiter was noticed. She recalled knowing of this goiter for more than 40 years. A CT scan showed severe pressure and narrowing of the trachea. Total thyroidectomy with sternotomy for the retrosternal goiter was performed as first step operation. Pathology reported of poorly differentiated thyroid carcinoma, arising in papillary thyroid carcinoma (PTC), follicular variant with capsular and vascular invasion.

Post-operative FDG PET-CT showed residual right neck mass with moderately to high uptake, multiple lung lesion with absent to low uptake, multiple lytic skeletal lesion with moderately to high uptake, and an intrathecal lumbar spine lesion with moderately to high uptake, summarized as metastatic PTC. In a second combined operation, the residual neck mass and the intrathecal lumbar spine lesion initially diagnosed as an ependymoma were removed. Pathology of both lesions was consistent with metastatic PTC.

Following this operation external beam radiation to the neck, skeletal lesions, and the lumbar spine was given followed by 150 mCi of ^{131}I. A post treatment scan showed high uptake in the lung and skeletal lesions. Clinically, she restored her walking ability and the back pain was improved.

Rates of Malignancy in Cytology Indeterminate Thyroid Nodules- A Single Center Surgical Series

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Background: The Bethesda system for reporting thyroid fine needle aspiration (FNA) cytology defines six categories, each carrying a specific risk for thyroid cancer. Categories III, IV and V have a reported rate of approximately 15%, 25% and 70% respectively and are considered indeterminate. The 2015 American Thyroid Association guidelines recommends for each center to define its categorical cancer risk.

Aim: To define cancer risk in cytologically indeterminate thyroid nodules in patients operated at the ENT department in Soroka University Medical Center (SUMC).

Methods: All patients undergoing total thyroidectomy or lobectomy at the ENT department in SUMC between 12/2013 and 9/2017 who had an indeterminate cytology (Bethesda category III-V) were included. Demographic, clinical, biochemical, cytological and pathological data were reviewed.

Results: 93 patients fulfilled inclusion criteria. Mean age was 50 years, 74% were female. Thirty nine (42%) were defined cytologically as Bethesda III, 33 (35%) Bethesda IV and 21 (23%) Bethesda V category. Malignancy rates for each category were 49%, 64%, 95% respectively. Among 60 patients with thyroid carcinoma, 52 (87%) had a pathological diagnosis of papillary thyroid carcinoma. One patient in category III and six in category IV had a pathological diagnosis of follicular thyroid carcinoma. One patient in category V had anaplastic carcinoma.

Conclusions: In SUMC indeterminate cytology by the Bethesda system showed higher malignancy rates than expected. This may be influenced by selection bias of patients referred to surgery due to other than cytology malignancy risk factors, but also raise the possibility of underreporting malignancy by the cytologist

Sexual Dimorphism of Size: Ontogeny and Life History

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Background: Sexual dimorphism in stature and weight is the outcome of boys and girls responding differently to environmental cues and may have fitness advantage because of the interaction between size-related survival and size–related obstetric complications and fertility.

Hypotheses: Living standard and health affect size dimorphism; Variations in size dimorphism are due to differential responding by boys and girls to environmental cues; Size dimorphism will be greater where population average height and weight are greater.

Methods: We characterized size dimorphism in the CDC2000 database from age 0-20. We correlated 161 countries' a-gross domestic product, b-life expectancy (LE), c-population average size with adult M/F ratio in height and weight per country. We correlated M/F height and weight ratio in 44 present-day preindustrial societies with LE, total population and density.

Results: Size dimorphism appears and disappears at minipuberty and then is established when the boys enter puberty. Stature and weight M/F ratio correlate with the LE (r=.572**, =.262*, resp.) and average M (r=.519**, =.523**) and F height (r=.183*, p=0.019, r=.299**), but not with the GDP. In 44 preindustrial societies, size dimorphism correlates positively with average M (r= .410*) but not F height, weight dimorphism correlates with the tribal population (r=-.534*).

Conclusions: Minipuberty is associated with adult-type size dimorphism. Size dimorphism is established during puberty. In industrial societies but not in preindustrial societies LE and living standards positively correlates with size dimorphism. Female's growth is more resilient to negative health effects. Size dimorphism is greater where human size is greater.

Early Growth in Relation to Family Size and Birth Rank

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Background: Among the most important environmental cues to child growth is the family structure. It was previously suggested that children in large families(LF) are shorter than those from smaller families(SF). We framed the hypothesis that family size and birth rank impact infantile(I) and childhood(C) growth, and the transition age between them(ICT).

Methods: In a cohort of 416 children of small families (6 children) and a control group (n=165), we determined the length at birth, I(6-7m), C(20-24m) and the ICT age.

Results: The study group subjects were significantly shorter than control at birth and at Childhood and their mean ICT age was later (11.9 vs.10.6m, p0.001). Within the study group, the last children (5^{th}) in LF were short at birth (-0.3 SDS), at infancy

(-0.4 SDS) and they lost additional 0.3 SDS at ICT age as compared to 0.03 SD in SF. Family size correlated significantly and negatively with birth, I and C length, and the birth rank correlated significantly and negatively with I and C length and positively with ICT age. The ICT age correlated strongly with the loss of height from I to C

(r=-.627, p0.0001) and with C length (r=-.361, p=0.0001);

Conclusions: Prenatal, infantile and mostly childhood length are compromised in children from LF. As the family grows larger the younger children get shorter. Family structure is a central mechanism for short stature in LF. Two components of family structure having negative influence on childhood length the family size and the birth order.

Economic Evaluation of Dapagliflozin as Add-on to Metformin for T2DM Treatment in the Israeli Healthcare Setting

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Aim: Dapagliflozin may be combined with metformin in T2DM treatment. However, its cost-effectiveness relative to other alternatives in the Israeli healthcare setup remains unknown. We aimed to evaluate the cost-effectiveness of dapagliflozin 10mg as add-on to metformin, compared to common anti-diabetic alternatives (sitagliptin 100mg, glimepiride 2mg, liraglutide 1.2mg) based on Meuhedet health services database.

Methods: A cost-effectiveness evaluation was performed using the Cardiff diabetes model. A cohort of 1000 T2DM patients (ages 21 and older), treated with metformin and an additional anti-diabetic medication, was randomly included from Meuhedet`s database. Simulation was performed for each drug, calculating its total costs and benefits (QALYs). The model`s time horizon was set to 40 years, annual discount rate for both costs and benefits was 3.5% and incremental cost effectiveness ratio (iCER) threshold was £20,000/QALY. Finally, single-variable and multivariable sensitivity analyses were performed.

Results: In the base-case scenario, dapagliflozin was found cost-effective compared to sitagliptin, liraglutide and glimepiride (iCER values of £1,232, £-16,517 and £13,476, respectively). For all comparisons, iCER was driven by differences in costs, while differences in QALYs were minimal. Dapagliflozin remained cost-effective even after performing sensitivity analyses. However, when performing the simulation under comparators` generic competition scenario, dapagliflozin was no longer cost-effective compared to liraglutide (iCER =£24,900/QALY).

Conclusions: Dapagliflozin as an add-on treatment to metformin was cost-effective compared to several alternatives for T2DM therapy in Israel`s healthcare system. Additional research is needed to evaluate the effects of evolving new clinical data.

Lipid Profile in Youth with T1DM: Evaluating Factors Contributing To Dyslipidemia

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Cardiovascular disease (CVD) is the leading cause of death in patients with T1DM. Dyslipidemia is an important CVD risk factor and is evident together with subclinical atherosclerosis even in the pediatric age. Glycemic control affects lipid profile.

Our aim was to evaluate lipid profile in children and young adults with T1DM.

We studied 227 youth with type 1 diabetes, 50% males, age 3-30 y (mean 14 ± 5.3 y) and age at diagnosis 8.2 ± 4.4 y. Patient`s data were collected during follow up of 6.0 years. Subjects with T1DM had repeated lipid measurements, mean 7, including: total cholesterol, HDL cholesterol, LDL cholesterol and Triglycerides. TG/HDL ratio was calculated. Age, sex, ethnicity, diabetes duration, body mass index and HbA1c were recorded. Predictors of LDL, HDL and TG were determined.

Dyslipidemia was equally found in boys and girls. Total cholesterol 200 was recorded in 32% of all patients, LDL was 100 mg/ dl in 62 %, HDL was 40 in 31%, TG 150 in 33%. Patients were divided into age tertiles: less than 10 years, 10-14 years, 14-18 years and 18 years. LDL was 50th percentile in 56%, 69 %, 72 %, 80% of patients, respectively, when compared to normal pediatric levels in those tertiles. TG / HDL ratio was 2 in 53%.

LDL correlated with HbA1C, regression coefficient = 0.17, p 0.0001.

Youth with T1DM demonstrate abnormal atherogenic lipid profile. Unfavorable glycemic control contributes to this profile. Studying other causes is needed.

Fracture Risk in Patients with Acute Poliomyelitis Going Through Late Adulthood

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Introduction: While OP fractures are reported in up to 40% of post-poliomyelitis adults, few data exist on the significance of BMD and best timing for initiating treatment.

Aims: In this ongoing study we aim to fill the gap on matters like early detection of high-risk patients and indications for treatment.

Methods: Historical prospective study, review-of-charts based.

Results: From 651 patients with poliomyelitis followed at our institution (mean age 64.6±8, females 49%), 125 patients had their charts reviewed and the preliminary data is presented. This group included 59 males and 66 females, mean age 64.4±7.2 (males 64.9±6.5, females 64±7.7) and median BMI 27 (20-44). Females were all postmenopausal except 3, with a median of 2 deliveries (range 0-4). The affected limbs were: legs 105/125 patients (right=33, left=35, both=37) and arms 14/125 (right=7, left=5, both=2). In 50 patients ≥1 limb was affected, including 10 having all 4 limbs affected. BMD was performed in 65.4% patients, median Tsc was: LS -0.8 (+1.3 to -2.7), affected leg -1.3 (-0.4 to -3.1), unaffected leg -1.2 (+0.4 to -2.5). Recurrent falls were recorded for 44% cases, OP for 45%, and OP any-time treatment 37.5%. Fracture data were available for 80 patients, 60% had at least one fracture, 13 of whom (16.2%) had ≥2 fracture and 9 (10%) ≥3 fractures.

Conclusion: OP in polio patients entering late adulthood appears underdiagnosed and undertreated despite their high risk for fragility fractures. This special population needs to be closely monitored and considered for anti-osteoporotic medication on time.

Long-Term follow up of Monthly Somatostatin Analogues Therapy in Pediatric Hypothalamic Obesity Patients

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Introduction Hypothalamic obesity (HO) is an intractable form of obesity caused by different etiologies both genetic and acquired disorders. Somatostatin analogues (SA) therapy have been described with efficacy and high safety profile in patients with neuroendocrine and pituitary diseases in the adult. Only few clinical trials reported the effect of SA in the pediatric population with HO and all were of short duration.

Objectives: To assess the long-term effects of SA therapy among children and youth with HO. Design and methods This is an observational retrospective multi-center study which included 6 medical centers in Israel.

Primary outcome: safety parameters, delta BMI(SDS) and height (SDS). Secondary outcome: changes in metabolic and laboratory parameters following SA therapy

Results: Study population included 11 patients (7 males), median age 16 years (range 9-20.4), 5 of them were fully pubertal. The etiologies of HO included 9 subjects after surgery for Craniopharyngioma (6) Astrocytoma (2) and Ependimoma (1), 1 patient with ROHHAD syndrome, and 1 with Hypothalamic Cortical Dysplasia . Median duration of treatment was 18 months (range 12-61). BMI (SDS) decreased significantly following SA therapy by -0.5 SDS (range -0.58 to -0.3) ,(p =0.017). There was no significant decrease in height median change 0 SDS (range-0.19- 0.6), and no differences in all the other parameters including pubertal progression and metabolic parameters following SA therapy.
Conclusion Therapy with SA is effective therapy in the attenuation of weight increase in pediatric patients with HO ,without decrease in growth rate and without metabolic abnormalities.

Topical Application of an Aqueous Nasal Steroids Solution as Effective and Safe in the Management of Skin Irritation Due to Continuous Glucose-Monitoring System Adhesives

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Background: Use of a continuous glucose-monitoring system (CGMS) in the management of type 1 diabetes (T1D) may cause local skin irritation.

Objective: To examine the clinical and metabolic effect of fluticasone propionate aqueous nasal solution (nsFP) , sprayed topically on the skin area prior to CGMS insertion.

Subjects: All patients treated in one center, who experienced skin irritation due to CGMS device and adhesives, who were offered this management.

Methods: This is a case-series observational report, including real life 6 months follow up data. Primary outcome; the difference in degree of skin irritation before and after use, according to the modified Draize scale. Secondary outcome; the change in BMI SDS, height SDS, mean glucose, and HbA1c after nsFP administration.

Results: The series included12 participants, mean age 8.6 ± 4.9 years, 66.7% males. Two patients had no improvement. Ten patients, median age 6.1 (5.3, 9.5), 56% males, demonstrated a positive response, with resolution of the local skin reaction. All were using the spray for a mean duration of 0.56 ± 0.11 years. No statistically significant differences were found in HbA1c 7.9(7.5,8.1) vs. 7.4(7-7.9), mean glucose 180(153,202) vs. 165(150-192), and number of daily prick tests 8.9(5.8,11.1) vs. 10.1 (8.9,13.5). BMI-SDS was non-significantly higher at the end of follow up 0.03(-0.22,0.93) vs. 0.44(-0.9,1),p=0.05. **Conclusions**: The simple use of an aqueous topical steroid spray on the skin may safely improve tolerance to CGMS devices in children and adolescents experiencing local reactions to the adhesives. Regular BMI assessment is recommended.

Symposia 5: Concept of Immunotherapy in Cancer

Endocrine Complications of Cancer Immunotherapies

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Hadassah Medical Center, Jerusalem

Cancer immunotherapy has revolutionized the field of oncology, providing an effective treatment for hematologic and solid malignancies considered otherwise untreatable. There are currently six immune checkpoint inhibitors approved by the FDA, including anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody (ipilimumab), anti-programmed cell death-1 (PD-1) antibodies (pembrolizumab, nivolumab), and anti-programmed cell death-1 ligand (PD-L1) antibodies (atezolizumab, durvalumab, avelumab). While immune checkpoint blockade can induce significant antitumor benefits, it can cause adverse effects through nonspecific immune enhancement. These adverse effects have been termed immune-related adverse events (irAEs), and include dermatologic, hematologic, neurologic, gastrointestinal, pulmonary and renal complications. Of particular interest is the development of immune-related endocrinopathies, most commonly acute hypophysitis especially with the anti-CTLA-4 drugs and thyroid diseases most frequently with the anti-PD-1/PD-L1 drugs. Other endocrinopathies including type 1 diabetes mellitus, primary adrenal insufficiency, primary hypogonadism and primary hypoparathyroidism have been reported although are rare. Consensus recommendations on identification, treatment and monitoring patients with irAEs, including endocrinopathies were recently published. As the indications for immune checkpoint inhibitor therapy are rapidly expanding, early identification and prompt treatment of irAEs is essential to afford patients the maximum benefit from these potentially lifesaving therapies. More evidence-based data should be obtained to guide the best clinical decision making.

Symposia 6: Treatment of Thyroid Disorders - A Different View

Role of T3 in the Treatment of Hypothyroidism - The Deiodinase Story

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Much progress has been made since the realization in the middle of the 19th century that myxedema and cretinism were linked to the thyroid gland. Until Murray's first attempt at treating myxedema with injections of sheep thyroid extracts in 1891, this condition was invariably fatal. Administration of dessicated thyroid extracts became the mainstay of hypothyroidism treatment until the mid-1970's. The change occurred after Barverman and Ingbar's demonstrated peripheral conversion of synthetic thyroxine (T4) to triiodothyronine (T3) when administered to athyreotic subjects. With the understanding that thyroxine is a pro-hormone, which could be conveniently dosed once daily, thyroxine became the preferred, and officially endorsed, replacement therapy for hypothyroidism. However, it also became clear that a fraction of patients who achieved normal TSH levels remained symptomatic, and that a subset displayed low circulating T3 concentrations.

The majority (~70%) of circulating T3 is derived from peripheral deiodination of T4 by type 2 deiodinase (DIO2), which is expressed in a variety of tissues including the thyroid gland itself, and the hypothalamus/pituitary. This enzyme is induced in hypothyroidism and inactivated by ubquitination. It has recently been shown that this ubiquitination is differently regulated in the hypothalamus. Indeed, hypothalamic conversion of T4 to T3 does not inactivate DIO2 as it does in the periphery, leading to locally generated T3 sufficient to suppress pituitary TSH secretion. This may provide an explanation to the low T3, normal or suppressed TSH situation encountered in some of the patients and offer the rationale for T3-supplemented treatment of hypothyroid subjects, particularly in athyreotic subjects.

Role of T3 in the treatment of hypothyroidism - Why, when and how?

Eyal Robenshtok
Rabin Medical Center, Beilinson Campus

Despite biochemical euthyroidism, some levothyroxine (L-T4) treated hypothyroid patients report persisting symptoms, and some of these patients are tentatively treated with a combination of L-T4 and liothyronine (L-T3). European Thyroid Association (ETA) guidelines from 2012 suggest that L-T4 /L-T3 combination therapy could be considered for compliant patients with persisting complaints despite normalized TSH values for 6 months, and no other medical conditions explaining the symptoms. In contrast, the 2014 American Thyroid Association (ATA) guidelines on hypothyroidism recommend treatment with L-T4 alone. This discrepancy, as well as conflicting studies in the literature, explain why L-T 4 /L-T3 combination therapy is still regarded as controversial among specialists.

In this talk we will review current literature, treatment guidelines, discuss suggested approach for patients selection, and propose a treatment protocol for L-T4 /L-T3 combination.

INDEX

A

B

C

D

H

I

J

K

L

M

N

O

P

R

S

T

Z