האגודה הישראלית לאנדוקרינולוגיה IES Israel Endocrine Society

The 48th Annual Meeting of the Israel Endocrine Society

April 7-8, 2019
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 48th annual meeting that will take place for the second time in a row at the beautiful, and conveniently located, Tel Aviv beach front Hilton hotel.
We are thrilled to announce that this year too, congress attendees will enjoy the participation of guest speakers from abroad, 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 you are all aware, the meeting had to be moved ahead by a day because of the early elections that were called for April 9th. Fortunately, the venue could host us as of April 7th, but some venue-related time constraints forced the executive committee to be creative and to shuffle the program around. In doing so we had to forego one plenary lecture, and to skip the lifetime recognition award we had the two previous years. We will make sure maintain those in coming meetings
This notwithstanding, we are in for an exciting program filled with wonderful science. As in the past, we will have 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 harnessing big data to the clinic, advances in the treatment of obesity, the connection between nutrition and reproduction, and the link between growth hormone and longevity.
We are extremely excited to announce that thanks to the ESE, this year congress will host for the second time the European Lecture that will be delivered by Dr. Felix Beuschlein from Zurich.
Among our guests from abroad will be Drs. Ira Goldberg, Nils Krone, Manuel Tena-Sempere, and John Kopchick, who will work hard to enlighten the congress attendees with plenary lectures, symposia and meet-the-expert sessions.
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.
As in the past, we will award our scientific prizes, the Chovers and Lindner awards, and for the second time we will honor a community endocrinologist for his/her contribution to the advancement of the profession.
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 every one 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

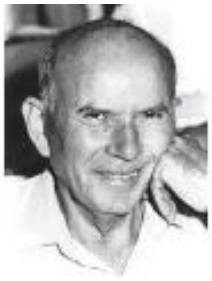
פרופ' הנס יוחנן לינדנר נולד בשנת 1922 בגרמניה ועלה ארצה עם הוריו בשנת 1936. לאחר מלחמת השחרור הוא למד רפואה וטרינארית בסידני (אוסטרליה) וסיים בהצטיינות. את לימודיו לתואר Ph.D. הוא השלים באוניברסיטת קיימבריג' שבאנגליה. עם תום לימודיו, חזר לינדנר לאוסטרליה, התמנה כחוקר בכיר ב- Commonwealth Scientific Research 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- דר' עמית אקירוב
2018 – פרופ' גד אשר

2019-דר' איל רובינשטוק

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 – סימונה גלסברג
2018 – דר' יוסי תם

2019- דר' יעל ריאחי

רופאת הקהילה המצטיינת לשנת 2019

ד"ר אלה (אלזביאטה) בראון

SUNDAY, APRIL 7, 2019

08:30-10:00 Thyroid I — Hall A
Chairs: Dania Hirsch, Carlos Benbasst

08:30 Thyroidectomy & Parathyroidectomy: TransOral Endoscopic TransVestibular Approach (TOETVA)
Avi Hefetz, Niddal Assadi, Eran Alon
A.R.M Clinics, A.R.M Otolaryngology Head and Neck & Maxillofacial Surgery

08:42 Urinary Iodine Content (UIC) and its Correlation to Maternal and Neonatal Thyroid Functions in Israel
Tal Schiller[1], Hilla Knobler[1], Arnon Agmon[2], Viviana Ostrovsky[1], Taiba Zornitzki[1]
[1]*Diabetes, Endocrinology and Metabolism Unit, Kaplan Medical Center*
[2]*Lev Tel-Aviv Women's Health Center, Clalit Health Services*

08:54 Thyroid Dysfunction and Mortality in Cardiovascular Hospitalized Patients – A 12 years Follow-up Observational Study
Meir Frankel[1], Feras Bayya[2], Rivka Farkash[2], Michael Glikson[2], Gabriel Munter[1]
[1]*Endocrinology Unit, Shaare-Zedek Medical Center*
[2]*Cardiology Department, Shaare-Zedek Medical Center*

09:06 Thyroglobulin and Anti-thyroglobulin Antibodies Following Lobectomy: Implications for Response to Therapy Restaging System
Amit Ritter[2,4], Gideon Bachar[2,4], Ilan Shimon[1,4], Dania Hirsch[1,4], Carlos Benbassat[3,4], Talia Diker-Cohen[1,4], Hadar Duskin-Bitan[1,4], Eyal Robenshtok[1,4]
[1]*Endocrinology Institute, Rabin Medical Center*
[2]*Department of Otorhinolaryngology, Head and Neck Surgery, Rabin Medical Center*
[3]*Endocrine Institute, Assaf Harofeh Medical Center*
[4]*Sackler Faculty of Medicine, Tel Aviv University*

09:18 Response to Therapy Assessment in Intermediate-Risk Differentiated Thyroid Cancer Patients – Is rhTSH Stimulation Required?
Itamar Moreno[2], Ilan Shimon[1,2], Dania Hirsch[1,2], Carlos Benbassat[2,3], Eyal Robenshtok[1,2]
[1]*Endocrinology Institute, Rabin Medical Center*
[2]*Sackler Faculty of Medicine, Tel Aviv University*
[3]*Endocrinology Department, Assaf Harofeh Medical Center*

09:30 PD-L1 Expression in Normal Endocrine Tissues
Maayan Kagan[3], Rena Pollack[1], Rivka Dresner-Pollak[1], Tzahi Neuman[2]
[1]*Endocrinology, Diabetes and Metabolism, Hadassah-Hebrew University Medical Center*
[2]*Pathology, Hadassah-Hebrew University Medical Center*
[3]*Hebrew University School of Medicine, Jerusalem,*

09:42 Clinical Characteristics and Long-term Follow-up of Patients with Congenital Hypothyroidism (CH) due to Thyroid Peroxidase (TPO) gene Mutations
***Nominee for Best Clinical Abstract Award**
Leraz Tobias2,3, Yardena Tenenbaum-Rakover1,3, Tal Almagor1,2,3, Shlomo Almashanu4, Morad Khayat5, Osnat Admoni1,3
1Pediatric Endocrine Institute, Ha'Emek Medical Center
2Pediatric Department B, Ha'Emek Medical Center
3The Rappaport Faculty of Medicine, Technion

4The National Newborn Screening Program, Ministry of Health, Tel Hashomer

08:30-10:00 Reproduction Hall B
Chairs: Talia Geva Eldar, Joseph Orly

08:30 Identification and Characterization of Novel Gonadotropin Gene Transcriptional Enhancers
***Nominee for Best Basic Abstract Award**
Tal Refael, Lilach Pnueli, Lilach Pnueli, Philippa Melamed, Philippa Melamed
Faculty of Biology, Technion-Israel Institute of Technology

08:42 Steroid Hormone Regulation of Tet1 Expression in Developing Gonadotropes
***Nominee for Best Basic Abstract Award**
Cfir David, Lilach Pnueli, Philippa Melamed
Biology, Technion - Israel institute of Technology

08:54 High Prevalence of Psychopathologies among Transgender Patients Presenting at a Large Tertiary Center: Implication for the Treating Clinicians
Gil Kerem1,2, Yona Greenman1,2, Iris Yaish1,2, Yael Sofer1,2, Nechama Golani1, Naftali Stern1,2, Karen Tordjman1,2
1*Institute of Endocrinology, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center*
2*Medicine, Sackler Faculty of Medicine*

09:06 Evidence for Preserved Ovarian Reserve in Transgender Men Receiving Testosterone Therapy: Anti-Mullerian Hormone Serum Levels Decrease Modestly After One Year of Treatment
Iris Yaish1, Gustavo Malinger2,3, Karen Tordjman1,3,
Foad Azem2,3, Yael Sofer1, Nechama Golani1, Naftali Stern1,3, Foad Azem,
Yona Greenman1,3
1*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center*
2*Lis Maternity Hospital, Tel Aviv-Sourasky Medical Center, Tel Aviv-Sourasky Medical Center*
3*Sackler School of Medicine, Tel Aviv University*

09:18 SIRT1 and Inflammatory Cytokines in Visceral Fat in Ovariectomized Mice - a Mouse Model of Human Menopause
Aviv Shabat1, Irina Gurt1, Einav Cohen-Kfir1,2, Oran Yakobovsky1,
Rivka Dresner-Pollak1
1*Endocrinology and Metabolism Department, Division of Medicine, Hadassah-Hebrew University Medical Center*
2*Institute of Medical Research Israel-Canada, Hebrew University-Hadassah Medical School*3

09:30 Primary Ovarian Insufficiency Incidence Rate and Etiology among Israeli Adolescents between the years 2000-2016 – A Nationwide Study
Noah Gruber1,2, Shir Kugler1,2, Liat de Vries1,3, Avivit Brener1,3, Amnon Zung4,5, Ori Eyal1,6, Marianna Rachmiel1,7, Ilana Koren8, Yardena Tenenbaum-Rakover9,10, Eli Hershkovitz11,12, Zohar Landau1,13, Meirav Oren14, Alon Eliakim1,15, David Zangen5,16, Alina German17, Hussein Majdoub8, Kineret Mazor-Aronovitch1,2, Dalit Modan-Moses1,2, Yonatan Yeshayahu1,2, Larisa Naugolni7, Yael Levy-Shraga1,2, Michal Ben-Ami1,2, Gherta Brill18,

Nehama Zuckerman-Levin10,19, Floris Levy-Khademi5,20, Carmit Avnon-Ziv5,20, Dov Tiosano10,14, Shira Harel21, Einat Kedem13, Anat Segev-Becker6, Yehuda Shoenfeld1,22, Orit Pinhas-Hamiel1,2
1*Sackler School of Medicine, Tel-Aviv University*
2*Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center*
3*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes,, Schneider Children's Medical Center of Israel*
4*Pediatric Endocrinology Unit, Kaplan Medical Center*
5*The School of Medicine, The Hebrew University of Jerusalem*
6*Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Children Hospital, Tel Aviv Sourasky Medical Center*
7*Pediatric Endocrinology Unit, Assaf Haroffeh Medical Center*
8*Pediatric Clinic, Armon Child Center, Clalit Health Services*
9*Pediatric Endocrine Unit, Ha'Emek Medical Center*
10*The Rappaport Endocrinology Faculty of Medicine, Technion*
11*Pediatric Endocrinology and Metabolic Unit, Soroka University Medical Center*
12*Israel and the Faculty of Health Sciences, Ben-Gurion University of the Negev*
13*Pediatric Endocrine and Diabetes Unit, E. Wolfson Medical Center*
14*Paediatric Endocrine Unit, Rambam Health Care Campus*
15*Pediatric Department, Meir Medical Center*
16*Division of Pediatric Endocrinology, Hadassah Hebrew University Medical Center*
17*Pediatric Department, Bnei Zion Medical Center*
18*Migdal Hamea, Clalit Health Services*
19*Institute of Diabetes, Endocrinology and Metabolism, Rambam Medical Center*
20*Division of Pediatric Endocrinology, Shaare Zedek Medical Center*
21*Central District, Maccabi Health Services*
22*Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer*

09:42 Estrogen Suppresses Left Ventricular Pro-fibrotic Gene Expression via Upregulation of miR-26a, 133a, 34a in Ovariectomized Mice

Elishai Assayag1, Irina Gurt1, Einav Cohen-Kfir1,3, Oran Yakobovsky1, Donna Zfat-Zwas2, Rivka Dresner-Pollak1
1*Endocrinology and Metabolism Department, Division of Medicine, Hadassah-Hebrew University Medical Center*
2*Linda Joy Pollin Cardiovascular Wellness Center for Women, Division of Cardiology, Hadassah-Hebrew University Medical Center*
3*Current affiliation: Institute of Medical Research Israel-Canada, Hebrew University-Hadassah Medical School*

08:30-10:00 Diabetes mellitus, Obesity — Hall C

Chairs: **Yonit Marcus- Perlman, Rosane Abramof-Ness**

08:30 Revisiting the Normal Body Mass Index among Ethiopian Adolescents: A Nationwide Study of 317,000 Males and Females.
***Nominee for Best Clinical Abstract Award**

Uri Hamiel[1,2], Cole Bendor[3,4], Aya Bardugo[3,4], Zivan Berr[3], Estela Derazne[2,3], Dorit Tzur[3], Ehud Grossman[2,5], Arnon Afek[2,5], Orit Pinhas-Hamiel[2,6], Gilad Twig[2,3,4,7]
[1]*Department of Pediatrics, Assaf Harofeh Medical Center*
[2]*Sackler School of Medicine, Tel-Aviv University*
[3]*Surgeon General Headquarters Defense Forces*
[4]*Department of Military Medicine, Hebrew University School of Medicine*
[5]*Central Management, Sheba Medical Center*
[6]*Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba*

Medical Center
[7]*Department of Medicine and the Dr. Pinchas Bornstein Talpiot Medical Leadership Program, Sheba Medical Center*

08:42 Severe Obesity and Cardiometabolic Comorbidities in Adolescents: Chronology of an epidemic

***Nominee for Best Clinical Abstract Award**

Gilad Twig[4,7] Tali Cukierman-Yaffe[8,9], Orit Pinhas-Hamiel[1], Brian Reichman[2], Arnon Afek[3], Estela Derazne[4], Uri Hamiel[5], Ariel Furer[4], Liron Gershovitz[4], Jeremy D. Kark[6], Tarif Baer[4],
[1]*Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center*
[2]*The Women and Children's Health Research Unit, Gertner Institute, Tel Hashomer*
[3]*Central Management, Chaim Sheba Medical Center, Tel Hashomer*
[4]*Medical Corps, The Israel Defense Forces*
[5]*Department of Pediatrics, Assaf Harofeh Medical Center*
[6]*School of Public Health and Community Medicine, Hebrew University-Hadassah*
[7]*The Dr. Pinchas Bornstein Talpiot Medical Leadership Program,, Sheba Medical Center*
[8]*Istitute of Endocrinology, Sheba Medical Center*
[9]*Sackler School of Medicine, Tel-Aviv University*

08:54 Epigenetic-changes in Response to Metabolic Modifiers in late-life: Exercise, High Fat Diet and Angiotenin1-7 Effects on Metabolic Health and DNA Methylation in Frail Old Mice

Gabi Shefer[1,2,5], Yonit Marcus[1,2], Elad Segev[3], Tamar Shahal[1,2,4,5],
Yuval Ebenstein[4,5], Naftali Stern[1,2,5]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Medical Center*
[2]*Sackler Faculty of Medicine, Tel Aviv University*
[3]*Department of Applied Mathematics, Faculty of Science, Holon Institute of thechnology*
[4]*Raymond and Beverly Sackler Faculty of Exact Sciences, School of Chemistry, Tel Aviv University*
[5]*Institute of Endocrinology, Metabolism and Hypertension, Sagol center for the epigenetics of metabolism and aging, Tel Aviv Sourasky Medical Center*

09:06 Circulating Endocannabinoids are Reduced following Bariatric Surgery and Associated with Improved Metabolic Homeostasis in Humans

Shahar Azar[1], Shiri Sherf-Dagan[2,3,4], Alina Nemirovski[1], Muriel Webb[2],
Asnat Raziel[5], Andrei Keidar[6], David Goitein[4,5,7], Nasser Sakran[5,8,9], Oren Shibolet[2,4],
Joseph Tam[1], Shira Zelber-Sagi[2,10]
[1]*The Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem*
[2]*Department Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv*
[3]*Department of Nutrition, Assuta Medical Center, Tel-Aviv*
[4]*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv*
[5]*Assia Medical Group, Assuta Medical Center, Tel-Aviv*
[6]*Department of General Surgery, Assuta Ashdod Public Hospital, affiliated to the Ben-Gurion University, Beer-Sheba*
[7]*Department of Surgery C, Sheba Medical Center, Tel Hashomer*
[8]*Department of Surgery A, Emek Medical Center, Afula, affiliated with Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa*
[9]*Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa*
[10]*School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa*

09:18 Abdominal Obesity as a Continuum: What is a Normal Waist Circumference in Israel?

Yonit Perlman[1,2], elad Segev[4], Gabi Shefer[1,2], Galina Shenkerman[1,2], Assaf Buch[1,2],
Shani Shenhar-Tsarfaty[2,3], David Zeltser[2,3], Itzhak Shapira[2,3],
Shlomo Berliner[2,3], Ori Rogowski[2,3], Naftali Stern[1,2]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Medical Center*

[2]*Sackler Faculty of medicine, Tel Aviv university*
[3]*Department of Medicine and Preventive Medicine, Tel Aviv Medical Center*
[4]*Department of Applied Mathematics, Faculty of Science, Holon Institute of Technology*

09:30 Therapeutic Efficacy of an Indoline Derivative in Preventing the Development of the Metabolic Syndrome
Anna Permyakova[1], Liad Hinden[1], Asaad Gammal[1], Marta Weinstock[2], Joseph Tam[1]
[1]*The Hebrew University of Jerusalem, Faculty of Medicine, Obesity and Metabolism Laboratory*
[2]*The Hebrew University of Jerusalem, Faculty of Medicine, Psychopharmacology laboratory*

09:42 Higher Insulin Degrading Enzyme levels In Subjects with the Metabolic Syndrome
Yael Sofer[1], Yuval Nash[2], Itai Benhar[3], Ofir Forsht[2], Esther Osher[1], Limor Nahary[2], Sigal Shaklai[1], Karen Tordjman, Merav Serebro[1], Elia-Belle Touati[1], Michal Yacobi Bach[1], Yonit Marcus[1], Brurya Tal[1], Jessica Sack[1], Gabi Shefer[1], Nathan Landis[1], Naftali Stern[1], Dan Frenkel[2]
[1]*Institute of Endocrinology, Metabolism and Hypertension and Sagol Metabolic Syndrome Research Center, Ichilov Sourasky Medical center and Sackler Faculty of Medicine*
[2]*Department of Neurobiology, Biochemistry and Biophysics George S Wise Faculty of Life Sciences and and Sagol School of Neuroscience, Tel Aviv University*
[3]*Department of Molecular Microbiology and Biotechnology, School of Molecular Cell Biology and Biotechnology, Tel Aviv University*

10:00-10:20 Coffee Break *Foyer*

11:20-12:10 Prize lectures — Hall A

Chair: Avraham Karasik

11:20 The Changing Face of Thyroid Cancer – Where do we go from here?
Eyal Robenshtok - **Recipient of Hans Lindner Prize Lecture**
Endocrinology & Metabolism Institute
Beilinson Hospital, Rabin Medical Center

11:35 Stressing Beta-Cells during the Neonatal Period Predisposes to Diabetes Later in Life
Yael Riahi **- Recipient of Israel Chowers Prize Lecture**
The Hebrew University- Hadassah Medical Center

11:50 Outstanding Community Physician Award - Elzbieta Baron, Endocrinology Kiryat Motzkin, Maccabi Healthcare Services

12:10-13:00 Plenary lecture 1 — Hall A

Chair: **Hannah Kanety**

Fat in the Blood, Fat in the Heart
Ira Goldberg
NYU School of Medicine, NYU Langone Health

13:00-14:00 Lunch *Foyer*

14:00-15:30 Symposia 1: CAH — Hall A

Chairs: **Naomi Weintrob, David Zangen**

14:00 Molecular Pathogenesis of Rare Forms of CAH
Nils P Krone

Academic Unit of Child Health Dep. of Oncology & Metabolism University of Sheffield; Sheffield Children's Hospital, Western Bank, UK

14:30 Genotype DOES Predict Phenotype in CAH Secondary to 21 -Hydroxylase Deficiency- The Israel Experience
Naomi Weintrob1, David Zangen2
1*Department of Pediatrics, Meir Medical Center*
2 *Hadassah Medical Center*

15:00 21-Hydroxylase Deficiency, Insights from the Molecular Lab and Implication for the Clinic
Adi Mory
Genetic Laboratory, Rambam Health Care Campus

14:00-15:30 Symposia 2
Big Data – Digital Health — Hall B
Chairs: **Moshe Phillip, Irit Hochberg**

14:00 Big Data: From Research to Value
Varda Shalev
Director of research and innovation institute Maccabi and Morris Kahn.
Tel Aviv university, Sackler School of Medicine

14:30 Changing the Landscape of Osteoporosis- Artificial Intelligence to Detect at-Risk Individuals
Shiri Salomon
Zebra Medical Vision

15:00 The Emerging Digital Diabetes -"Clinic"
Eran Atlas
CEO, DreaMed Diabetes

15:30-15:50 Coffee Break — *Foyer*

15:50-16:50 Meet the Expert — Hall A

Novel Avenues in the Management of Congenital Adrenal Hyperplasia
Nils P Krone
Academic Unit of Child Health Dep. of Oncology & Metabolism University of Sheffield; Sheffield Children's Hospital, Western Bank, UK

15:50-16:50 Meet the Expert — Hall B

Endocrine Hypertension
Felix Beuschlein
University Hospital of Zurich

16:50-17:30 IES Members General Assembly — Hall A
Executive Committee Report
Accountant Report

MONDAY, APRIL 8, 2019

07:30-08:00 Registration and Gathering ***Foyer***

08:00-09:30 Bone Metabolism — Hall A

Chairs: **Pnina Rotman, Yankel Gabet**

08:00 Denosumab-induced Hypocalcemia in Patients with Osteoporosis- Can You Know Who Will Get Low? Retrospective Analysis of Real-world Data

Gloria Tsvetov1,3, Oren Amitai1,3,5, Tzippy Shochat2, Amit Akirov1,3, Talia Diker-Cohen1,3,4

1*Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center - Beilinson Hospital*

2*Statistical Consulting Unit, Rabin Medical Center - Beilinson Hospital*

3*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv*

4*Medicine A, Rabin Medical Center - Beilinson Hospital*

5*Clalit Health Services, Dan-Petah-Tikva district.*

08:12 Magel2 Modulates Bone Remodeling and Mass in Prader Willi Syndrome by Affecting Oleoyl Serine Levels and Activity

Saja Baraghithy1, Reem Smoum2, Adi Drori1, Rivka Hadar1, Asaad Gammal1, Shira Hirsch1, Malka Attar-Namdar3, Alina Nemirovski1, Yankel Gabet4, Yshaia Langer5, Yehuda Pollak5, Christian Patrick Schaaf6,7, Megan Rech7, Varda Gross-Tsur5, Itai Bab3, Raphael Mechoulam2, Joseph Tam1

1*Obesity and Metabolism Laboratory, The Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem*

2*Medicinal Chemistry Laboratory, The Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem*

3*Bone Laboratory, Institute for Dental Research, Faculty of Dentistry, The Hebrew University of Jerusalem*

4*Department of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel-Aviv University*

5*Neuropediatric Unit, Department of Pediatrics, Shaare Zedek Medical Center*

6*Department of Molecular and Human Genetics, Baylor College of Medicine, USA*

7*Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, USA*

08:24 Sex-specific Regulation of Bone Resorption in the Osteoclast Lineage by Krox20: Hormone-independent Sexual Dimorphism

Elias Sabag1, Elinor Halperin1, Tamar Liron1, Sahar Hiram-Bab1, Baruch Frenkel2, Yankel Gabet1

1*Department of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel Aviv University*

2*Departments of Biochemistry and Molecular Medicine and Orthopedic Surgery, Keck School of Medicine of the University of Southern California, USA*

08:36 The Association between Glycemic Control and Hip Fracture Risk- A Retrospective Cohort Study

Uri Yoel1,3, Noa Zimhony-Nissim2,3, Victor Novack2,3, Merav Fraenkel1,3
1*Endocrinology, Soroka University Medical Center*
2*Clinical Research Center, Soroka University Medical Center*
3*Faculty of Health Sciences, Ben-Gurion University of the Negev*

08:48 The Impact of Diabetes Mellitus on Survival after Hip fracture a Single Center Experience

Vitaly Medvedovsky1, Roni Gat2, Uri Yoel1, Lior Baraf1, Dayana Cohen1,
Tamar Eshkoli1, Victor Novack2, Ethel Siris3, Merav Fraenkel1
1*Endocrinology, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev*
2*Clinical Research Center, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev*
3*Endocrinology, Columbia University Medical Center, USA*

09:00 Trabecular Bone Score (TBS) Change is Not Predicted by Bone Turnover

Genya Ahahron-Hananel1, Galia Zakay2, Iris Vered1, Liana Tripto-Shkolnik1
1*Osteoporosis service, Endocrine Institute, Sheba Medical Center, Tel Hashomer*
2*Meuhedet, Health Fund*

09:12 Low Trabecular Bone Score with or without Osteoporosis is Differentially Linked to Distinct Clinical Conditions.

Vanessa Rouach1,2, Mira Arbiv1, Iris Yaish1, Naomi Even-Zohar1, Naftali Stern1,2
1*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv Sourasky Medical Center*
2*Sackler Faculty of Medicine, Tel Aviv University*

08:00-09:30 Diabetes, Basic and Clinical — Hall B

Chairs: **Sigal Shaklai, Amir Tirosh**

08:00 Parenteral Cephalosporins and Parenteral Glucose During the Neonatal Period are Associated with Pediatric Type 1 Diabetes Development
***Nominee for Best Basic Abstract Award**

Iren Zargari1,2, Adi Adar1,2, Rimona Keidar2,3, Ori Eyal3,4, Neta Loewenthal5,
Orit Pinhas-Hamiel2,6, Iris Morag2,7, Milana Levy8, Orna Dally-Gottfried9,
Zohar Landau2,10, Floris Levy-Khademi11,12, David Zangen11,13,
Smadar Eventov-Friedman11,14, Ilan Youngster2,15, Marianna Rachmiel1,2
1*Pediatric Endocrinology Unit, Division of Pediatrics, Assaf Harofeh Medical Center*
2*Sackler School of Medicine, Tel Aviv University*
3*Neonatal Intensive Care Unit, Assaf Harofeh Medical Center*
4*Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Children Hospital, Tel Aviv Sourasky Medical Center*
5*Pediatric Endocrinology and Metabolic Unit, Soroka University Medical Center*
6*Pediatric Endocrinology and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer*
7*Neonatal Intensive Care Unit, Sheba Medical Center, Tel Hashomer*
8*Pediatric diabetes and Obesity Clinic, Ruth Rappaport Children`s Hospital, Rambam Health Care Campus*
9*The Center for Juvenile Diabetes and Pediatric Endocrinology and Pediatric Outpatient Clinics, Rebecca Ziv Hospital, Safed, affiliated to The School of Medicine, Bar Ilan University*
10*Pediatric Endocrinology and Diabetes Unit, E. Wolfson Medical Center*
11*The School of Medicine, The Hebrew University of Jerusalem*
12*Division of Pediatric Endocrinology, Shaare Zedek Medical Center*
13*Division of Pediatric Endocrinology, Hadassah Hebrew University Medical Center*
14*Neonatal Intensive Care Unit, Hadassah Hebrew University Medical Center*
15*Infectious diseases Unit, Assaf Harofeh Medical Center*

08:12 Endoplasmic Reticulum (ER) Stress Inhibits Insulin/IGF-1 Signaling in β-cells and Hepatocytes by Reducing P85α Expression

Roni Yeroslaviz1, Yael Riahi1, Aviram Kogot-Levin2, Tal Israeli1, Erol Cerasi1, Boaz Tirosh3, Gil Leibowitz1

1*Endocrinology and Metabolism, The Hebrew University-Hadassah Medical School, Jerusalem*

2*The Diabetes Unit, Hadassah-Hebrew University Medical Center, Jerusalem*

3*The School of Pharmacy, The Hebrew University of Jerusalem*

08:24 Pediatric Type 1 Diabetes Mellitus Incidence rate and Socioeconomic Ranking in Israel

Hila Ben Ezri Yitzhak1, Moshe Shirav-Schwartz2, Orit Blumenfeld3, Jonathan Dubnov4, Shai Linn4, Wasef Nhamnih3, Ilana Koren1

1Pediatric Diabetes Clinic Armon Child Center, Clalit Health Services

2(emeritus), Geological survey of Israel

3Gertner institute, Chaim Sheba Medical Center

4School of Public Health, Haifa University

08:36 Why Should We Measure Low Density Lipoprotein Cholesterol Directly? Comparison between Plasma LDL-Cholesterol Assessment by Friedewald Equation and Direct Measurement

Hofit Cohen1,2, Dror Harats1,2, Aviv Shaish1,3, Joseph Roitelman1,2

1*Chaim Sheba Medical Center, The Bert W. Strassburger Lipid Center*

2*Tel Aviv University, Sackler Faculty of Medicine*

3*Academic College, Achva*

08:48 SGLT2 Inhibition Ameliorates Diabetic Nephropathy by Inhibiting mTORC1 in a Mouse Model of Type 1 Diabetes

Aviram Kogot-Levin1, Ofri Mosenzon1, Liad Hinden3, Yael Riahi2, Erol Cerasi2, Joseph Tam3, Gil Leibowitz2

1*The Diabetes Unit, Hadassah-Hebrew University Medical Center, Jerusalem*

2*The Diabetes Unit and the Endocrine Service, Hadassah-Hebrew University Medical Center, Jerusalem*

3*Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, Jerusalem*

09:00 Diabetic Ketoacidosis (DKA) induced by Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2-i) : The Israeli experience

Meir Frankel2,3, Einat Gorelik1, Eli Marom1

1*Pharmaceutical Division, Ministry of Health*

2*Endocrinology unit, Shaare-Zedek Medical Center*

3*Diabetes & Endocrinology Clinic, Clalit Health Institute*

09:12 The Relationship Between Maternal Glucose Variability During Pregnancy & Neonatal Birthweight Percentile in Pre-Gestational Diabetic Women

Nimrod Dori-Dayan1, Tali Cukierman-Yaffe2, Roni Zemet1, Shali Mazaki-Tovi1, Rakefet Yoeli-Ulman1

1*Gynecology and Obstetrics, Sheba Medical Center*

2*Endocrinology, Sheba Medical Center*

08:00-09:30 Neuroendocrinology and Adrenal — Hall C

Chairs: **Ester Osher, Ilan Shimon**

08:00 Endoscopic Ultrasound Guided Radiofrequency Ablation (EUS-RFA) as a Novel Therapeutic Approach in Highly-Selected Pancreatic Neuroendocrine Neoplasms (pNENs) Patients: Preliminary Report.

Kira Oleinikov1, Allen Dancour2, Julia Epshtein3, Ariel Benson3, Haggi Mazeh4, Ilanit Tal1, Dan Meir Livovsky2, Eran Goldin2, David J Gross1, Harold Jacob3, Simona Grozinsky-Glasberg1

1Neuroendocrine Tumor Unit, ENETS Centre of Excellence, Endocrinology & Metabolism, Hadassah-Hebrew University Medical Center, Ein Kerem

2*The Gastroenterology Institute, Shaare Zedek Medical Center*

3*Department of Gastroenterology, Hadassah-Hebrew University Medical Center, Ein Kerem*
4*Department of Surgery, Hadassah-Hebrew University Medical Center, Mount of Scopus*

08:12 Molecular and Functional Investigation of the Differential Regulation of LH and FSH Cells in Fish

Lian Hollander-Cohen1, Matan Golan2, Patrice Mollard2, Berta Levavi-Sivan1
1*Animal Sciences, Hebrew University*
2*Institut de G'nomique Fonctionnelle, CNRS, UMR-5203, France*

08:24 Tissue Turnover Dynamics in the HPA Axis Explains the Timescale of Weeks in Clinically Relevant Conditions

Avichai Tendler1, Alon Bar1, Netta Mendelson Cohen2, Lior Maimon1, Yael Korem1, Omer Karin1, Avraham Mayo1, Uri Alon1
1*Molecular cell biology, Weizmann Institute of Science*
2*Computer Science, Weizmann Institute of Science*

08:36 Anatomic Site of Pancreatic Neuroendocrine Tumors as a Prognostic Marker

Muhamad Badarna1,2, Amit Tirosh1,2, Ruth Percik1,2
1*Neuroendocrine Tumors Service, Endocrine Institute, Chaim Sheba Medical Center*
2*Sackler Faculty of Medicine, Tel-Aviv University*

08:48 Ovarian adrenal rest tumors in congenital adrenal hyperplasia: Is medical treatment the first line option?

Ronit Koren1,6, Shlomit Koren2,3,6, Alla Khashper4,6, Carlos Benbassat2,6, Marina Pekar-Zlotin5,6, Zvi Vaknin5,6
1*Department of Internal Medicine A, Assaf Harofeh medical center*
2*Endocrine Institute, Assaf Harofeh medical center*
3*Diabetes unit, Assaf Harofeh medical center*
4*Department of diagnostic imaging, Assaf Harofeh medical center*
5*Department of Obstetrics and Gynecology, Assaf Harofeh medical center*
6*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv*

09:00 Hyperandrogenism in a 13-year-old Girl due to Glucocorticoid Receptor Mutation

Osnat Admoni1, Dani Bercovitch2, Yardena Tenenbaum-Rakover1,3
1*Pediatric Endocrine Institute, Ha'Emek Medical Center*
2*Galilee Genetic Analysis Lab, Tel Hai College*
3*Rappaport Faculty of Medicine, Technion*

09:12 Posterior Pituitary Spindle-cell Oncocytoma: Case Presentation and Literature Review

Naomi Even-Zohar1, Touati Elia-Belle1, Naftali Stern1,2, Yona Greenman1,2
1*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky medical center*
2*Sackler School of Medicine, Tel Aviv University*

09:30-09:50 Coffee Break — *Foyer*

09:50-10:40 Plenary lecture 2 — Hall A

Chairs: Naftali Stern

Recent Advances in Deciphering the Genetic Basis of Endocrine Hypertension

Felix Beuschlein, The ESE Lecture
University Hospital of Zurich

10:40-12:10 Symposia 3

Lipids Inflammation and Atherosclerosis — Hall A

Chair: **Hilla Knobler, Hofit Cohen**

10:40 Diabetes, Lipids, and Macrovascular Complications

Ira Goldberg
NYU School of Medicine, NYU Langone Health, USA

11:10 Lipoprotein a: When to Measure and How to Treat?
Hilla Knobler
Diabetes, Endocrinology & Metabolism Institute, Kaplan Medical Center, Rehovot

11:40 Targeting Inflammation for Prevention of Recurrent Cardiovascular Events
Yehuda Kamari
Sheba Medical Center, Ramat Gan

10:40-12:10 Symposia 4
New Directions in Growth Hormone-IGF1 Research — Hall B

Chairs: **Haim Werner; Yona Greenman**

10:40 GH Effects on Fat in Humans and Mice; Cellular Impact and 'Big Data'
John Kopchick
Edison Biotechnology Institute, Ohio University; Athens, OH, USA

11:10 " Longevity: is taller better?"
Gil Atzmon
University of Haifa and Albert Einstein College of Medicine, NY

11:40 The Role of the IGF1 Pathway in Neurodegenerative Disorders: Mechanisms and Therapeutic Opportunities
Ehud Cohen
The Hebrew University of Jerusalem

12:10-13:10 Prizes for Best Abstracts and Posters
Plenary lecture 4 — Hall A

Chair: **Zvi Laron**

12:20
Growth Hormone, Mini-mice, Football, Dirty Shorts, and a New Drug
John Kopchick
Ohio University, USA

14:10-15:40 Symposia 5
Mechanisms of Metabolic Surgery and Incretin Therapies for Diabetes and Obesity — Hall A

Chairs: **Gil Leibowitz, Benjamin Glaser**

14:10 Sleeve Gastrectomy Improves Glycemia Independent of Weight Loss
Danny Ben Zvi
The Hebrew University of Jerusalem

14:40 GIP Regulation of Body Weight and Inflammation
Sigal Fishman
Sourasky Medical Center, Tel Aviv

15:10 The Present and Future of Incretin Therapies for Obesity and Diabetes
Ofri Mosenzon
The Diabetes Unit Hadassah University Hospital, Ein Kerem; Jerusalem

14:10-15:40 Symposia 6
Central Control of Reproductive Function — Hall B

Chairs: Philippa Melamed; Adi Avrech

14:10 Early-life Stress and Effects on Adult Reproductive Function
Philippa Melamed
Faculty of Biology, Technion Institute of Technology, Haifa

14:40 Metabolic-Reproductive Connections: Molecular Basis for Disordered Puberty in Malnutrition and Obesity
Manuel Tena-Sempere
Physiology Section, Faculty of Medicine University of Cordoba, Spain

15:10 Gonadotropins Role in Mediating the Medical Complications of Anorexia Nervosa
Dalit Modan
Pediatric Endocrinology and Diabetes Unit, The Edmond and Lily Safra Children's Hospital,Sheba Medical Center

15:40-15:50 Coffee Break — *Foyer*

15:50-16:50 Meet the Expert — Hall A

Lipid Disorders
Ira Goldberg
NYU School of Medicine, NYU Langone Health

POSTER SESSION

10:20-11:20 Poster Presentation — Poster Hall

1. Urinary Free Cortisol Levels and Risk of Recurrence or Persistence of Cushing's Syndrome Related to Primary Bilateral Macronodular Adrenal Hyperplasia

Leonard Saiegh1, Ibrahim Mattar2, Carmela Shechner1, Maria Reut1, Jacob Bejar3, Monica Laniado2, Mohammad Sheikh-Ahmad1

1*Institute of Endocrinology, Bnai Zion Medical Center*
2*Surgery department, Bnai Zion Medical Center*
3*Institute of Pathology, Bnai Zion Medical Center*

2. Central Precocious Puberty as Presenting Sign of Non-Classical Congenital Adrenal Hyperplasia - Prevalence and Clinical Characteristics

Bar Neeman1, Rachel Bello1,2, Liora Lazar1,2, Moshe Phillip1,2, Liat de Vries1,2

1*Sackler faculty of medicine, Tel-Aviv university*
2*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel*

3. A Seminoma with Entrapped Nerve Ganglion Masquerading as a Paraganglioma

Rachel Chava Rosenblum1, Karine Atlan2, Judith Diment2, Haggi Mazeh3, Pnina Rotman-Pikielny1, Orit Twito1

1*Endocrinology Institute, Meir Medical Center*
2*Department of Pathology, Hadassah-Hebrew University Medical Center*
3*Department of Surgery, Hadassah-Hebrew University Medical Center*

4. Pheochromocytoma: Positive Predictive Values of Mildly-elevated Urinary Fractionated Metanephrines and Current Features at Diagnosis.

Dania Hirsch1,3,4, Alon Grossman2,3,4, Varda Nadler5, Sandra Alboim5, Gloria Tsvetov1,3,4

1*Endocrine Institute, Rabin Medical Center*
2*Department of Internal Medicine B, Rabin Medical Center*
3*Sackler Faculty of Medicine, Tel Aviv University*
4*Endocrinology, Maccabi Health Care Services*
5*Central Laboratory, Maccabi Health Care Services*

5. Higher C-peptide Levels and Glucose Requirements may Identify Neonates with Transient Hyperinsulinism Hypoglycemia Who Will Benefit from Diazoxide Treatment

Anita Schachter Davidov1, Erella Elkon-Tamir1, Gabi Shefer3, Naomi Weintrob1, Asaf Oren1, Yael Lebenthal1, Dror Mandel2, Ori Eyal1

1*Pediatric Endocrinology Unit, Dana-Dwek Children's Hospital, Tel-Aviv Sourasky Medical Center*
2*Department of Neonatology, Dana-Dwek Children's Hospital, Tel-Aviv Sourasky Medical Center*
3*The Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center*

6. A Short Pheochromocytomas (PCC) and Paragangliomas (PGL) PPGLs Series from a 2018 Perspective

Inna Tkacheva1, Efrat Markus1, Shlomit Koren1,2, Carlos Benbassat1,2, Miriam Steinschneider1,2

1*Endocrine Institute, Assaf Harofeh Medical Center*
2*Sackler Faculty of Medicine, Tel-Aviv University*

7. Prevalence of Diabetes among Children Treated with Growth Hormone in Israel
***Nominee for Best Clinical Poster Award**

Miri Lutski1, Inbar Zucker1,2, Zvi Zadik3, Carmit Libruder1, Orit Blumenfeld1, Tamar Shohat1,2, Zvi Laron4

1*Israel Ministry of Health Center for Disease Control*
2*Tel Aviv University, Department of Epidemiology and Preventive Medicine, School of Public Health,*
Sackler Faculty of Medicine
3*Kaplan Medical Center, Pediatric Endocrinology Unit and Chairman Research Authority*
4*Schneider Children's Medical Center, Endocrinology and diabetes Research Unit*

8. ProGRP is an Effective Marker for Disease Monitoring in Lung Carcinoids with Non-Informative Chromogranin A: Lessons from Clinical Practice

Kira Oleinikov1, Simona Grozinsky-Glasberg1, David J Gross1, Hovav Nechushtan2, Tamar Peretz2, Ofra Maimon2, Benjamin Nisman2
1*Endocrinology & Metabolism Department, Neuroendocrine Tumor Unit, ENETS Centre of Excellence, Hadassah-Hebrew University Medical Center, Ein Kerem*
2*Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Ein Kerem*

9. **Lower All-cause Mortality Rates in Patients Harboring Pituitary Carcinoma (PitCa) Following the Introduction of Temozolomide**
Genya Ahahron-Hananel, Ruth Percik, Amit Tirosh

10. **Three Years Persistence with Denosumab as Osteoporosis Therapy in Maccabi Healthcare Services**
Naama Fund1, Inbal Goldshtein1, Vanessa Rouach1,2, Gabriel Chodick1,3, Varda Shalev1,3
1*Institute of Research and Innovation, Maccabi healthcare services*
2*Institute of endocrinology, Tel Aviv Sourasky medical center*
3*Sackler Faculty of Medicine, Tel Aviv University*

11. **The Enigma of Unexpected High BMD in an Anorectic Patient**
Matan Elami-Suzin1, Meir Liebergal2, Yusuf Azrak3, Rivka Drezner Pollak1, Hamutal Gur4
1*Endocrinology, Hadassah Ein Kerem*
2*Orthopedics, Hadassah Ein Kerem*
3*Radiology, Hadassah Ein Kerem*
4*Rheumatology, Hadassah Ein Kerem*

12. **Bone Loss under Oral Bisphosphonates Treatment in Maccabi Healthcare Services**
Naama Fund1, Inbal Goldshtein1, Vanessa Rouach1,2, Michal Guindy3, Gabriel Chodick1,4, Varda Shalev1,4
1*Institute of Research and Innovation, Maccabi healthcare services*
2*Institute of endocrinology, Tel Aviv Sourasky medical center*
3*Imaging Department, Assuta medical center*
4*Sackler Faculty of Medicine, Tel Aviv University*

13. **Hypophosphatemia Following a Ferric Carboxymaltose Injection: an FGF-23 Mediated Process**
Liana Tripto-Shkolnik1, Iris Vered1, Ehud Barhod2, Pazit Zilber2, Amir Tirosh1, Rina Hemi2
1*Division of Endocrinology, Diabetes and Metabolism, Chaim Sheba Medical Center, Tel-Hashomer*
2*Endocrine Laboratory, Chaim Sheba Medical Center, Tel-Hashomer*

14. **Longitudinal Follow-up of Bone Density in Children with Inflammatory Bowel Diseases**
Yael Levy-Shraga1,2, Anatoli Shenkar2, Amit Assa2, Dalit Modan1,2, Yael Haberman2, Dror Shouval2, Anat Guz-Mark2, Avishay Lahad2, Batia Weiss2
1*Pediatric Endcrinology and Diabetes Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center*
2*The Sackler Faculty of Medicine, Tel-Aviv University*

15. **Characterization of a Series of Subjects with Pregnancy and Lactation-associated Osteoporosis (PLaOP) in Israel**
Vanessa Rouach1,2, Mira Arbiv1, Karen Tordjman1,2
1*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center*
2*Internal Medicine, Sackler Faculty of Medicine*

16. **Pseudohypoparathyroidism- A Tale of Hypo and Hypercalcemia with a Genetic Solution**
Rachel Chava Rosenblum1, Yael Einbinder2, Orit Twito1, Giovanna Mantovani3, Francesca Elli3, Pnina Rotman-Pikielny1
1*Endocrinology Institute, Meir Medical Center*
2*Nephrology Institute, Meir Medical Center*
3*Endocrinology and Diabetology Unit, University of Milan, Italy*

17. **Connexin-43 Mediated Cell-cell Communication and Propagation of Adipose Tissue ER Stress in Obesity**
***Nominee for Best Basic Poster Award**
Sophie T. Ron1,2, Idit Ron1, Moran Rathaus1, Rinat Livne1, Nissim Oz1, Assaf Rudich3, Amir Tirosh1,2

1*The Dalia and David Arabov Endocrinology and Diabetes Research Center, The Institute of Endocrinology, Sheba Medical Center*
2*Sackler Faculty of Medicine, Tel-Aviv University*
3*Faculty of Health Sciences, Joyce and Irvin Goldman Medical School, Ben Gurion Universiry*

18. New Autosomal Dominant Mutation in Glucokinase Gene Causing Congenital Hyperinsulinism

Ilana Koren1, Amir Peleg2, Lena Sagi-Dain2, Amalia Harari-Shaham2, Gal Larom-Kahan2, Ben Glaser3
1Pediatric Endocrinology Clinic, Carmel Medical Center
2Human Genetic Institute, Carmel Medical Center
3Endocrinology and metabolism Service Internal Medicine Department, Hadassah Hebrew University Medical Center

19. Familial clinical heterogeneity manifested by the presence of either diabetes or deafness in a pedigree of a patient with Maternally Inherited Diabetes Mellitus and Deafness

Jessica Sack, Maya Ish Shalom, Michal Yaacobi, Naftali Stern
Endocrinology, Tel-aviv Soraski medical center

20. Towards Implementation of St. Vincent Declaration – Outcomes of Pre-gestational Diabetic Women Pregnancies

Nimrod Dori-Dayan1, Rakefet Yoeli-Ulman1, Neomi Kedar2, Ohad Cohen2, Tali Cukierman-Yaffe2
1*Gynecology and Obstetrics, Sheba Medical Center*
2*Endocrinology, Sheba Medical Center*

21. Diurnality, Type 2 Diabetes, and Depressive-like Behavior

Carmel Bilu1,2, Paul Zimmet3, Vicktoria Vishnevskia-Dai4, Haim Einat5, Galila Agam2, Ehud Grossman4, Noga Kronfeld-Schor1
1*School of Zoology, Tel Aviv University*
2*Department of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev*
3*Department of Medicine, Monash University, Australia*
4*Sackler Faculty of Medicine, Tel-Aviv University*
5*School of Behavioral Sciences, Tel Aviv-Yaffo Academic College*

22. Hospital discharge of diabetic patients and fulfillment recommendations for the diabetes management in outpatient therapy.

Elena Chertok Shacham, Ronit Nitzan, Avraham Ishay
Endocrinology Unit, Emek Medical Center Afula

23. The Role of the Adipokine FABP4 in the Pathophysiology of Gestational Diabetes

Ragad Mdah1,3, Roni Zemet2, Idit Ron1, Shali Mazaki-Tovi2,3, Amir Tirosh1,3
1*The Dalia and David Arabov Endocrinology and Diabetes Research Center, The Institute of Endocrinology, Sheba Medical Center*
2*Department of Obstetrics and Gynecology, Sheba Medical Center*
3*Sackler Faculty of Medicine, Tel-Aviv University*

24. The Association between Glycemic Control and Mortality- A Retrospective Cohort Study

Uri Yoel1,3, Noa Zimhony-Nissim2,3, Victor Novack2,3, Merav Fraenkel1,3
1*Endocrinology, Soroka University Medical Center*
2*Clinical Research Center, Soroka University Medical Center*
3*Faculty of Health Sciences, Ben-Gurion University of the Negev*

25. High Risk for Diabetic Foot Ulcer among Hospitalized Patients.
***Nominee for Best Clinical Poster Award**

Shlomit Koren1, Moriah Sharabi2, Tamar Moriel Levy2, Daniel Fux1, Ronit Koren3, Micha J. Rapoport2
1*Diabetes unit, Assaf Harofe Medical Center*
2*Department of Internal Medicine C, Assaf Harofe Medical Center*
3*Department of Internal Medicine A, Assaf Harofe Medical Center*

26. Heterozygous RFX6 Mutation as a Cause of Diabetes Mellitus in a Multigenerational Family

Nehama Zuckerman Levin1,4, Tamar Paperna2, Tova Hershkovitz2,4, Ady Mory2, Alina Kurolap2,4, Jamal Mahamid3, Hagit Baris Feldman2,4, Naim Shehadeh1,4

1*Pediatric Diabetes Clinic, Institute of Diabetes, Endocrinology and Metabolism, Rambam Health Care Campus*
2*The Genetics institute, Rambam Health Care Campus*
3*Pediatric clinic, Meuhedet health services*
4*The Ruth and Bruce Rappaport Faculty of Medicine, Technion*

27. Outcomes of Community-acquired Sepsis in Patients with Diabetes: A Retrospective Population-based Cohort Study.

Yarden Zohar1,6,7, Shani Zilberman2,6,7, Shlomit Koren3,4,6,7, Ronit Zaidenstein1,6,7, Dror Marchaim5,6,7, Ronit Koren1,6,7
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2*Department of Nephrology, Assaf Harofeh Medical Center*
3*Endocrine Institute, Assaf Harofeh Medical Center*
4*Diabetes Unit, Assaf Harofeh Medical Center*
5*Unit of Infectious Diseases, Assaf Harofeh Medical Center*
6*Assaf Harofeh Medical Center, Zerifin*
7*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv*

28. The Relationship between Low Carbohydrate Diet & Pregnancy Outcomes in Women with Pre-Gestational Diabetes- A Historical Prospective Study

Roy Shalit1, Nimrod Dori Dayan2, Rakefet Yoeli-Ullman2, Tali Cukierman-Yaffe1,3
1*Endocrinology Institute, Sheba Medical Center*
2*Obstetrics and gynecology, Sheba Medical Center*
3*Epidemiology Department, Sackler School of Medicine, Tel-Aviv university*

29. Igfbp1 as a Repression Target of PGC-1α in the Context of Blood Glucose Homeostasis

Neri Minsky
Institute of Endocrinology, Sheba Medical Cente

30. Antibody-negative Insulin-dependent Diabetes in Two Patients Treated with Immune Checkpoint Blockade

Tal Schiller1, Lyudmila Lysyy2, Taiba Zornitzki1, Viviana Ostrovsky1, Hilla Knobler1
1*Diabetes, Endocrinology and Metabolism Unit, Kaplan Medical Center*
2*Endocrinology Unit, Maccabi Health Services*

31. Atypical Presentation of Type 1 Diabetes Mellitus

Mark Niven1, Esther Kafri1, Elizabeth Nissim2, Ina Dubin2
1*Endocrine and Diabetes Unit, Laniado Hospital*
2*Internal Medicine A, Laniado Hospital*

32. Insulin Treatment is Associated with Improved Fetal Placental Vascular Circulation in Obese and Non Obese Women with Gestational Diabetes Mellitus.

Marina Shargorodsky2,3, Julia Barda1,2, Jacob Bar1,2
1*Gynecology, Wolfson Medical Center*
2*Sackler Faculty of Medicine,, Tel Aviv University,*
3*Endocrinology, Wolfson Medical Center*

33. The Association Between Obesity and Secular Trend of Stature: A Nationwide Study of 2.8 Million Adolescents over Five Decades.

Neta Geva1,2, Orit Pinhas-Hamiel3,4, Brian Reichman4,5, Estela Derazne1,4, Asaf Vivante4,6, Yair Barak4, Arnon Afek4,7, Amir Tirosh4,8, Gilad Twig1,4,9,10
1*Surgeon General Headquarters Defense Forces*
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3*Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center*
4*Sackler School of Medicine, Tel Aviv university*
5*The Women and Children's Health Research Unit, Gertner Institute*
6*Department of Pediatrics B, Edmond and Lily Safra Children's Hospital, Sheba Medical Center*
7*Central Management, Chaim Sheba Medical Center*
8*Institute of Endocrinology, Chaim Sheba Medical Center*
9*Department of Medicine and the Dr. Pinchas Bornstein Talpiot Medical Leadership Program, Chaim Sheba Medical Center*
10*Department of Military Medicine, The Hebrew University*

34. RNA-Seq Analysis of Ovariectomy-Induced Changes in Mouse Liver Reveals New Targets for Menopause-Associated Metabolic Derangement
***Nominee for Best Clinical Poster Award**
Joshua Stokar, Irina Gurt, Einav Cohen-Kfir, Oran Yakubovsky, Hanna Artsi, Elishai Assayag, Rivka Dresner-Pollak
Endocrinology and Metabolism, Hadassah & Hebrew University Medical Center

35. Identification of ZYG11A as a Novel Target for IGF1 Action in Endometrial Cancer Cells
Laris Achlaug1, Rive Sarfstein1, Karthik Nagaraj1, Lena Lapkina1, Zvi Laron2, Haim Werner1
1*Department of Human Molecular Genetics and Biochemistry, Tel Aviv University*
2*Endocrine and Diabetes Research Unit, Schneider Children's Medical Center*
The 48th Annual Meeting of the Israel Endocrine Society

36. Is There a Correlation Between miRNA hsa-132-3p Expression and Longevity in Laron Syndrome Patients?
Danielle Yaron-Saminsky1, Karthik Nagaraj1, Metsada Pasmanik-Chor2, Zvi Laron3, Haim Werner1
1*Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University*
2*Bioinformatic Unit, George Wise Faculty of Life Sciences, Tel Aviv University*
3*Endocrine and Diabetes Research Unit, Schneider Children's Medical Center*

37. Treatment Landscape for active Acromegaly in a Pituitary Centre in Israel
Hiba Masri-Iraqi1,2, Amit Akirov1,2, Ilan Shimon1,2
1*Endocrinology, Rabin Medical Center- Beilinson Campus*
2*Sackler Faculty of Medicine, Tel Aviv University*

38. Patients with Congenital IGF-1 Deficiency Have an Abnormal Plasma Amino Acid Pattern Partially Reversed by IGF-1 Treatment
Zvi Laron1, Chen Barazani2
1*Endocrinology and Diabetes Research Unit, Schneider Children's Medical Center*
2*Metabolic Laboratory, Schneider Children's Medical Center*

39. The Second to Fourth Digit Ratio in Patients with Congenital Igf-1 Deficiency
Zvi Laron1, Yoav Uchitel3, Rivka Kauli2, Osnat Konen4, Pearl Lilos5
1*Endocrinology & Diabetes Unit, Schneider Children's Medical Center*
2*Endocrinology and Diabetes, Schneider Children's Medical Center*
3*Endocrinology and Diabetes, Schneider Children's Medical Center*
4*Imagining Department, Schneider Children's Medical Center*
5*Statistics Unit, Schneider Children's Medical Center*

40. Combined Autophagy and mTOR Inhibition Reduces Cells Proliferation and Induces Apoptosis in a Lung Carcinoid In-Vitro Model
Adi Knigin1, Shani Avniel-Polak2, David Joseph Gross2, Simona Grozinsky-Glasberg2
1*Internal Medicine A, Hadassah-Hebrew University Medical Center*
2*Neuroendocrine Tumor Unit, ENETS Center of Excellence, Endocrinology Department, Hadassah-Hebrew University Medical Center*

41. Distinct Activities of IGF1R and INSR on ERK and AKT Signaling Pathways in Breast Cancer Cells
Rive Sarfstein, Haim Werner
Department of Human Molecular Genetics and Biochemistry, Tel Aviv university

42. Pregnancy in 17 Hydroxylase Deficiency
***Nominee for Best Clinical Poster Award**
Zeev Blumenfeld1, Ilana Koren2
1*Faculty of medicine, Technion*
2*Pediatric endocrinology, Clalit medical services*

43. Percutaneous Ethanol Injection Treatment for Thyroid Cysts
Pinchas Klein, Mark Niven
Endocrine Unit, Laniado Medical Center

44. Subclinical Hypothyroidism and All-Cause Mortality among ST Segment Elevation Myocardial Infarction Patients Undergoing Percutaneous Coronary Intervention
Elena Izkhakov1, David Zahler2, Keren-Lee Rozenfeld2, Dor Ravid2, Shmuel Banai2,

Yan Topilsky2, Naftali Stern1, Yacov Shacham2
1*Institute of Endocrinology, Metabolism and Hypertension, Tel-Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel-Aviv University*
2*Department of Cardiology, Tel-Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel-Aviv University*

45. Familial Non-medullary Thyroid Carcinoma Has Similar Presentation and Disease Outcome than Sporadic Non-medullary Thyroid Carcinoma
Miriam Steinschneider1,3, Shlomit Koren1,3, Karen Or1, Efrat Markus1, Carlos Benbassat1,3, Limor Muallem Kalmovich2,3
1*Endocrine Institute, Assaf Harofeh Medical Center*
2*Department of ENT, Assaf Harofeh Medical Center*
3*Sackler Faculty of Medicine, Tel-Aviv University*

46. Presentation of Thyrotoxicosis in Hospitalized Elderly Patients
Hadar Duskin-Bitan1,3, Chagit Adler-Cohen1, Ayelet Ferder2,3, Ilan Shimon1,3, Alon Grossman2,3
1*Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center*
2*Medicine B, Rabin Medical Center*
3*Sackler Faculty of Medicine, Tel Aviv University*

47. Adherence to Active Surveillance and Clinical Outcomes in Patients with Indeterminate Thyroid Nodules Who Are Not Referred for Thyroidectomy
Dania Hirsch1,3, Ilana Slutzky-Shraga1,3, Eyal Robenshtok1,3, Carlos Benbassat2,3,Alex Gorshtein1,3
1*Endocrine Institute, Rabin Medical Center*
2*Endocrine Institute, Assaf Harofeh Medical Center*
3*Sackler Faculty of Medicine, Tel Aviv University*

48. Surveillance of Patients with Differentiated Thyroid Cancer: The Impact of Stimulated Thyroglobulin Measurement with or without Whole-body Scan
Sharon Giveon1, Sigal Levy2, Pnina Rotman3, Rachel Rosenblum3, Orit Twito3
1*Department of Internal Medicine D, Meir Medical Center*
2*Statistics Education Unit, The Academic College of Tel Aviv-Yaffo*
3*Institute of Endocrinology, Meir Medical Center*

49. Thyroid Function Dynamics in Cancer Patients Treated with Immunotherapy
Amit Tirosh, Ruth Percik
Endocrine Institute, The Chaim Sheba Medical Center

50. Two Distinct Cyp19a1 Gene Promoters are Utilized Differently in Ovary and Hypothalamus for Driving Expression of Aromatase
***Nominee for Best Basic Poster Award**
Dor Shalev, Lilach Pnueli, Philippa Melamed
Faculty of Biology, Technion-Israel Institute of Technology

51. A Curious Case of Thyrotoxicosis
Mark Niven1,2, Ina Dubin2, Elizabeth Nissim2, Menachem Shapira3
1*Endocrinology and Diabetes, Laniado Hospital, Israel*
2*Internal medicine A, Laniado Hospital, Israel*
3*Endocrinology, Leumit Health Services*

52. Fine Needle "Parathyroidectomy"
Pinchas Klein, Mark Niven
Endocrine unit, Laniado Medical Center

53. Amiodarone-induced Thyrotoxicosis: A Late, Prolonged and Serious Complication
Yakov Rosen1, Hilla Knobler1, Tal Schiller1, Viviana Ostrovsky1, Lana Turkot2, Lyudmila Lysyy3, Taiba Zornitzki1
1*Diabetes, Endocrinology and Metabolic Disease Institute, Kaplan Medical Center, Hebrew University*
Medical School of Jerusalem
2*Endocrinology Unit, Barzilai Medical Center*
3*Endocrinology Unit, Maccabi Healthcare Services*

Thyroid I (Sunday, April 7, 2019 08:30)

Thyroidectomy & Parathyroidectomy:

TransOral Endoscopic TransVestibular Approach (TOETVA)

Avi Hefetz, Niddal Assadi, Eran Alon
A.R.M Clinics, A.R.M Otolaryngology Head and Neck & Maxillofacial Surgery, Israel

Introduction: The trans-cervical approach has been the primary route of access for thyroid and parathyroid gland since its description by Kocher 140 years ago. Several approaches have been suggested for minimizing the surgical scar but none of them have become common practice. Thus, a role for a new novel technique still exists for improving surgical esthetic outcome. The Trans-Oral Endoscopic Trans-Vestibular approach (TOETVA) has been recently reported as a novel approach for extraction of thyroid or parathyroid tumors.

Aim: To show the feasibility and safety of TOEVTA for thyroid and parathyroid surgery in Israel.

Methods: Case series of patients undergoing TOEVTA for Thyroidectomy and Parathyroidectomy at our institution. The study was approved by the IRB. **Results:**Twenty two patients (11 thyroidectomies and 11 parathyroidectomies) underwent TOETVA and were included. Average time of surgery was 3.3 hours. One patient had transient vocal cord paralysis, second patient had altered sensation of chin, third patient had seroma that resolved by aspiration. The same patient also had a skin laceration which was closed primarily with excellent healing. Surgery was successful in all patients with no permanent complications.

Conclusion: We report the first series of patients in Israel undergoing TOETVA for thyroid and parathyroid tumors. The learning curve is steep but improving. Surgery was uneventful and safe. The results are comparable withprevious reports.

Urinary Iodine Content (UIC) and its Correlation to Maternal and Neonatal Thyroid Functions in Israel

Tal Schiller[1], Hilla Knobler[1], Arnon Agmon[2], Viviana Ostrovsky[1], Taiba Zornitzki[1]
[1]*Diabetes, Endocrinology and Metabolism Unit, Kaplan Medical Center, Israel*
[2]*Lev Tel-Aviv Women's Health Center, Clalit Health Services, Israel*

Introduction

An Israeli national survey found that 85% of pregnant women had UIC levels below adequacy range (150mcg/L). Heavy reliance on desalinated water and lack of national fortification plan were suggested causes. Few studies assessed the correlation between iodine status to maternal and neonatal thyroid functions with varying results.

Aim

To determine whether iodine deficiency was associated with altered thyroid functions or autoimmunity in pregnancy, factors leading to iodine deficiency and neonatal outcome.

Methods

A cross-sectional study including 100 healthy women in their first trimester of a singleton pregnancy were recruited from an HMO clinic in central Israel. Women were followed from their first trimester. All women fulfilled detailed dietary and life habits questioners. We tested for UIC, maternal and neonatal thyroid functions, maternal autoantibodies and neonatal outcomes.

Results

Median UIC in our cohort was 49 mcg/L, corresponding to 84% below adequacy range. No correlation was found between Iodine deficiency and maternal or neonatal thyroid functions which remained within the normal range. Antibody status did not differ but thyroglobulin levels were significantly higher with iodine insufficiency. There was a significant correlation between multivitamin consumption and higher UIC. Water source nor Iodine consumption could account for the difference.

Conclusions

In our cohort, iodine deficiency did not affect maternal thyroid functions and antibody status, nor neonatal outcomes. This might reflect enough iodine to maintain normal function even in light of iodine deficiency. Only 60% of women reported taking a multivitamin. This issue needs to be addressed during the first prenatal visit.

Thyroid Dysfunction And Mortality In Cardiovascular Hospitalized Patients – A 12 years Follow-up Observational Study

Meir Frankel[1], Feras Bayya[2], Rivka Farkash[2], Michael Glikson[2], Gabriel Munter[1]
[1]*Endocrinology Unit, Shaare-Zedek Medical Center, Israel*
[2]*Cardiology Department, Shaare-Zedek Medical Center, Israel*

BACKGROUND

Thyroid dysfunction is associated with increased cardiovascular morbidity and mortality. Early detection may influence the clinical management of the patients. There is insufficient data about the prevalence and clinical significance of thyroid dysfunction in cardiovascular hospitalized patients.

AIMS

To study the prevalence and clinical significance of thyroid dysfunction in cardiovascular hospitalized patients.

METHODS

A retrospective analysis of a medical records` database of all adult patients admitted not-electively to the Cardiology Department at Shaare-Zedek Medical Center, between 2005-2017. Thyroid function test (TFT) was performed as a routine test in all patients.

RESULTS

During the described period there were 19281 non-elective hospitalizations of 14388 patients. TFT was available for 14384 patients during their 1st hospitalization, mean age 67±15. Thyroid dysfunction was present in 10% of the patients (2% TSH10mIU/L; 5% TSH 5-10mIU/L; 2% TSH 0.1-0.35mIU/L; 1% TSH 0.1mIU/L). The prevalence of thyroid dysfunction was significantly higher in elderly patients (age70y, 12.1%, Odds ratio[OR]=1.4) and in patients with atrial flutter/fibrillation (14%, OR=1.4), pulmonary hypertension (14%, OR=1.4), chronic renal failure (14%, OR=1.5), heart failure (15%, OR=1.5), hypothyroidism treated with Levothyroxin (28%, OR=3.3) and patients treated with Amiodarone (24%, OR=3). Adjusted multivariable analysis showed increased mortality for TSH0.35mIU/L, TSH 5-10mIU/L and TSH10mIU/L (1.6, 1.3 and 1.5, respectively).

CONCLUSION

The prevalence of thyroid dysfunction in cardiac hospitalized patients is 10% and it is higher in specific patient-groups. Thyroid dysfunction is associated with an increased mortality rate. Screening for thyroid function should be considered in cardiology departments, especially in selected high risk groups.

Thyroglobulin and Anti-thyroglobulin Antibodies Following Lobectomy: Implications for Response to Therapy Restaging System

Amit Ritter[2,4], Gideon Bachar[2,4], Ilan Shimon[1,4], Dania Hirsch[1,4], Carlos Benbassat[3,4], Talia Diker-Cohen[1,4], Hadar Duskin-Bitan[1,4], **Eyal Robenshtok**[1,4]

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Background: Response to therapy assessment tool is well validated for patients with thyroid cancer following total-thyroidectomy and radioiodine, but limited data is available for patients treated with lobectomy.

Methods: Patients who had lobectomy for DTC, followed for 1 year without completion thyroidectomy, and had sufficient data on Tg and TgAb.

Results: A total of 167 patients met inclusion criteria. Lobectomy was performed for classic papillary thyroid cancer (PTC) in 69%, follicular variant PTC in 29%, and other variants in 2%. Average tumor size was 9.5±6mm. Following lobectomy, Tg was 12.1±14.8ng/ml. Of 52 patients with HT, 38% had positive TgAb with titers of 438±528IU/mL, and 69% had no TgAb, with Tg levels of 13.5±18.4ng/ml. In 30 patients with contralateral nodules ≥1cm, Tg was 15.3±17ng/ml. During the first two years of follow-up, Tg declined ≥1 ng/ml in 40% of patients (by 6.5±6.2ng/ml), remained stable in 25%, and increased in 35% (by 5±5.7ng/ml). During 78±43.5 months of follow-up, 18 patients had completion thyroidectomy and twelve diagnosed with contralateral cancer (n=8) or lymph node metastases (n=4). In patients with recurrence followed for 2 years, there was a steady rise in Tg in three cases, Tg was stable in two cases, and in one TgAb decreased from 1534 to 276 despite metastatic lymph-node. Basal Tg and Tg dynamics did not predict disease recurrence.

Conclusions: Thyroglobulin used independently is of limited value to predict or detect locoregional recurrence following lobectomy. Other potential roles of Tg, such as excluding distant metastases following lobectomy should be further studied.

Response to Therapy Assessment in Intermediate-Risk Differentiated Thyroid Cancer Patients – Is rhTSH Stimulation Required?

Itamar Moreno[2], Ilan Shimon[1,2], Dania Hirsch[1,2], Carlos Benbassat[2,3], Eyal Robenshtok[1,2]
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Introduction: The 2015 ATA guidelines recommend response to therapy assessment using rhTSH stimulation 1-2 years following initial treatment in thyroid cancer patients to guide TSH goals and long term follow-up. We hypothesize that data collected during the first year of follow-up may be sufficient to determine response to therapy without Tg-stimulation.

Aim: To determine what is the added value of stimulated-Tg over data collected during the first year of follow-up to predict long-term risk of recurrence/persistence in intermediate-risk patients.

Methods: Patients treated with total-thyroidectomy and RAI for intermediate-risk DTC, followed for 2 year, who had sufficient follow-up data.

Results: 120 patients met inclusion criteria, with age of 55±15 years. Histology was PTC in 88%, follicular carcinoma in 10% and Hurthle-cell carcinoma in 2%. Follow-up duration was 7±4 years. Based on imaging and stimulated-Tg, 66% had excellent-response to therapy, with long term recurrence rate of 96%. When analyzed without stimulated-Tg, the percentage of patients with early "excellent response" (ER) was dependent on Tg threshold: with threshold of Tg1ng/ml, Tg0.6ng/ml or Tg0.2ng/ml there was 75%, 58%, and 48% ER rates. Excellent response with threshold of 0.6ng/ml and 0.2ng/ml were equally predictive of long term disease free rates of 96% and 95% respectively. Threshold of 1ng/ml was less predictive with long term disease free rate of 93%.

Conclusions: In patients with no evidence of disease during the first year of follow-up, the addition of stimulated-Tg adds little prognostic information. We suggest a modified definition of excellent response to therapy based on suppressed Tg.

PD-L1 Expression in Normal Endocrine Tissues

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Introduction: Immune checkpoint inhibitor (ICI) therapy, including cytotoxic T-lymphocyte-associated protein 4 (CLTA-4) and programmed cell death 1 (PD-1) inhibitors, is revolutionizing cancer treatment. However, these agents are associated with immune-related adverse events (irAEs), most commonly endocrine-related. Hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus and primary adrenal insufficiency have been reported as irAEs due ICI therapy. The precise mechanisms underlying these endocrine irAEs remain to be elucidated.

Aim: In this study, we evaluated patterns of programmed cell death ligand 1 (PD-L1) expression in normal endocrine tissues to determine whether increased expression may explain the predilection of endocrinopathies in patients treated with PD-1 inhibitors.

Methods: Immunohistochemical (IHC) analysis using the Ventana 22C3 PD-L1 IHC platform was performed on normal FFPE endocrine tissue samples stored in the Hadassah-Hebrew University pathology tissue archive.

Results: Five samples from each organ including pituitary, thyroid, parathyroid, adrenal and pancreas were examined. Focal membranous PD-L1 positivity was noted in the normal pituitary tissues, but was negative in normal thyroid, parathyroid, adrenal and pancreatic tissues.

Conclusions: Majority of normal endocrine tissues do not demonstrate increased PD-L1 expression. Our limited data so far does not support the hypothesis that increased PD-L1 expression in endocrine tissues is associated with the endocrine irAEs following anti PD-1 therapy. The increased predilection of endocrinopathies in patients treated with anti PD-1 inhibitors seems to be via alternate pathways.

Clinical Characteristics and Long-term Follow-up of Patients with Congenital Hypothyroidism (CH) due to Thyroid Peroxidase (TPO) gene Mutations

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Backround: Hereditary inborn error in thyroid hormone synthesis account for 10-20% of congenital hypothyroidism (CH). Thyroid peroxidase (TPO) deficiency is the most common enzymatic defect with a frequency of 50-90% of the cases. **Aim**: In the present study our objective was to characterize the long term clinical outcome in patients with TPO deficiency and to assess the association between development of multi nodular goiter (MNG) and the adherence to therapy. **Methods:** Clinical and genetic data was collected retrospectively from birth up to 44 years from the medical files of patients with TPO deficiency that are being followed at the Endocrine clinic at Ha`Emek Medical Center. **Results:** Thirty-tree patients from 15 nuclear families of Arab-Muslim Descent were enrolled. All patients had CH due to TPO deficiency. The main symptoms at presentation were neonatal jaundice (36%), macroglossia (27%) and umbilical hernia (27%), respectively. At 1 year follow up 9 (27%) showed a delay in developmental milestones, although the majority had normal cognitive achievements at time of the study. Three different mutations were identified by Sanger sequencing in the *TPO* gene at either homozygous or compound heterozygous form. At diagnosis, 4 patients presented with goiter, however over time, 61% developed MNG (61%), of these 7 underwent thyroidectomy and one had follicular thyroid carcinoma. **Conclusions:** Our cohort is the largest to date of patients with *TPO* mutations. The high rate of MNG developing with time and the risk for thyroid carcinoma indicates the need for long-term follow-up in these patients.

Identification and Characterization of Novel Gonadotropin Gene Transcriptional Enhancers

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The recent advances in high-throughput sequencing have revealed numerous non-coding RNAs (lncRNAs), some of which are transcribed from transcriptional enhancers and are thus termed eRNAs. Although the precise function of these is still poorly understood, knockdown of the gonadotropin α-subunit (*Cga*) distal enhancer eRNA led to a drop in *Cga* mRNA levels, dramatically altered the local and distal chromatin landscape and disrupted enhancer-promoter interactions. Currently we are aiming to identify multiple enhancer elements regulating basal or hormonally-stimulated gonadotropin gene expression, examine their functions and study how they can be manipulated to alter gene expression. We have discovered a putative upstream enhancer of the *Lhb* gene, which is transcribed into lncRNA, carries the enhancer-enriched H3K4me1 histone modification, and was found in physical contact with the proximal *Lhb* promoter. Stable cell lines expressing CRISPR dCas9-KRAB/VP64 with gRNAs targeting this region demonstrated significantly altered *Lhb* mRNA and eRNA expression. Moreover we have detected, using circular dichroism, a unique DNA structure in this region, and are currently verifying its role in the enhancer function. In order to identify additional eRNAs, we have performed RNA-seq on the chromatin-associated and cytosolic RNAs expressed in the gonadotropes. By combining this data with ATAC-seq data on the open regulatory regions, and localization of characteristic enhancer histone modifications, we have also revealed a novel putative enhancer for *Fshb*. Identification and characterization of these enhancers and the development of tools for altering their activity, should allow us to manipulate hormonal expression levels and thus possibly also activity of this axis.

Steroid Hormone Regulation of Tet1 Expression in Developing Gonadotropes

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TET1 plays a key role in epigenetic regulation during development, through directing the hydroxymethylation and demethylation of regulatory DNA of some genes while, paradoxically, also directly repressing the expression of others. We showed previously that TET1 is expressed in the expanding gonadotrope population of neonatal and adult gonadectomized mice, but is barely expressed in intact adult mice, possibly suggesting its negative regulation by gonadal steroids. Therefore, we hypothesized that TET1 is involved in the regulation of gonadotrope proliferation that is induced by steroid withdrawal. In this study, we show that the expression level of *Tet1* alters during the gonadotrope cell cycle, likely indicating a role in this process. Furthermore, we found that estrogen and androgen lower *Tet1* expression, and bind directly to its promoter through their respective receptors (ESR1 and AR). To further understand this regulation, we examined estrogen and androgen effects on the chromatin structure and the mRNA stability of *Tet1*. Chromatin immunoprecipitation revealed that exposure to estradiol (E2) or dihydrotesosterone (DHT) did not appear to alter the level of histone H3 association with the *Tet1* promoter. Moreover, the E2 treatment increased the level of active histone modification H3K27ac at the *Tet1* enhancer and promoter. In contrast, treatment with either steroid significantly decreased the half-life of *Tet1* mRNA by approximately 40%. These results suggest that steroid hormones confer dynamic regulation of *Tet1* expression during the proliferation and differentiation of gonadotrope precursor cells and thus likely play a crucial role in establishing this population of cells.

High Prevalence of Psychopathologies among Transgender Patients Presenting at a Large Tertiary Center: Implication for the Treating Clinicians

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Background and Aim of study: Endocrinologists may be ill-prepared to recognize and manage psychological disorders that may complicate gender dysphoria. We sought to characterize those in the population treated at our Transgender Health Clinic in the last 10 years, and to address the question of possible differences between transwomen (TW) and transmen (TM).

Methods: In this retrospective cohort study, all pertinent demographic and clinical data were retrieved from clinic charts.

Results: The cohort consisted of 405 subjects, 221 TW, and 184 TM (TW:TM=1.2:1), followed for of 2.4±0.1 y. TM were younger 26.1±7.3 vs 31.3±11, and presented at a younger age 23.6±7.2 vs 29.1±10.7 than TW (P

Conclusions: Our findings highlight the need to prepare endocrinologists for the high prevalence and severity of psychopathologic conditions in transgender people. A mental health professional should be an essential part of any multidisciplinary team of clinicians treating the transgender population.

Evidence for Preserved Ovarian Reserve in Transgender Men Receiving Testosterone Therapy: Anti-Mullerian Hormone Serum Levels Decrease Modestly After One Year of Treatment

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Background: Although successful pregnancies carried by transgender men have been reported, long-term effects of testosterone therapy on fertility remain unknown.

Aims: To study markers of ovarian reserve during testosterone therapy.

Methods: Prospective open-label study of transgender men prior and during treatment with testosterone. Sampling was conducted at baseline and 12 months after treatment initiation.

Main outcome measures: Anti-Mullerian Hormone (AMH), gonadotropins and sex steroid serum levels; endometrial thickness and antral follicular count determined by pelvic US.

Results: 52 subjects (23.4±6.1 y) were recruited, 32% of which were in a stable relationship. 17% expressed desire to have children while 26 (50%) were unsure about future parenthood. Four (7%) have already undergone fertility preservation procedures. Interestingly, 5 participants (9%) that initially were sexually attracted to women became bisexual under testosterone treatment.

Complete data is available for 32 subjects. In the course of 12 months of treatment, AMH levels decreased from 5.65±0.52ng/ml at baseline to 4.89±0.65 ng/ml (p=0.036). Antral follicular count (16.9±1.4, 13.9±1.7) and endometrial thickness (6.9±0.7, 5.6±0.5 mm) remained unchanged. As expected, testosterone levels increased (0.84±0.1, 7 ±0.7 nmol/l; p0.0001) and estradiol levels decreased (90.8±7.9, 55.4±4.6 pmol/l; p=0.0013) during therapy, with a concomitant decrease in LH (7.56±0.7, 3.8±0.6 mIU/ml; p=0.0012), but not FSH (5.1±0.41, 4±0.3; p=0.07 mIU/ml) levels.

Conclusion: AMH levels slightly decrease during testosterone treatment but remain within the normal, "healthy" range, thus likely indicating well-preserved ovarian reserve. This assumption is corroborated by the unchanged antral follicular count. The significance of these findings on fertility potential remains to be explored.

SIRT1 and Inflammatory Cytokines in Visceral Fat in Ovariectomized Mice - a Mouse Model of Human Menopause

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Introduction: Menopause is associated with increased visceral fat and unfavorable metabolic profile. Visceral fat induces the production of pro-inflammatory cytokines resulting in chronic low-grade inflammation. Sirtuin1 (Sirt1), a NAD^+-dependent deacetylase has beneficial metabolic effects and inhibits inflammation. We previously reported that Sirt1 is decreased in bone and liver in ovariectomized (OVX) mice, an established mouse model of human menopause. A previous study demonstrated that increased visceral fat tumor necrosis factor-α (TNF-α) in obesity leads to decreased Sirt1 via its cleavage.

Aim: To test whether OVX in mice is associated with reduced Sirt1 in visceral fat as a result of increased pro-inflammatory cytokines.

Methods: Nine week-old C57BL female mice (n=10/group) were subjected to OVX or SHAM operation and were sacrificed 6 weeks later. Visceral fat was collected and total RNA was extracted. Relative gene expression was determined by the comparative CT method. Protein level was determined by immunoblotting.

Results: OVX mice experienced a dramatic early weight gain. Sirt1 protein was decreased while Sirt1 mRNA expression was significantly increased in visceral fat in OVX compared to SHAM mice. No change in Sirt1 C-terminal fragment was observed, suggesting no cleavage. No difference in TNF-α was found, however, IL-1β and IL-6 were higher in OVX compared to SHAM mice.

Conclusions: Our data suggest that OVX is associated with decreased Sirt1 in visceral fat due to post translational mechanisms. The decrease in Sirt1 is not caused by elevated TNF-α. The effects of IL-1β and IL-6 on Sirt1 remain to be investigated.

Reproduction (Sunday, April 7, 2019 08:30)

Primary Ovarian Insufficiency Incidence Rate and Etiology among Israeli Adolescents between the years 2000-2016 – A Nationwide Study

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Introduction: Primary ovarian insufficiency (POI) occurring in youth is a devastating condition. POI is characterized by at least 4 months of disordered menses in association with menopausal follicle stimulating hormone (FSH) levels. Data are scarce regarding the incidence of POI in adolescents.

Aims: We estimated the current incidence and the distribution of etiologies of POI in a nationwide study in Israel.

Methods: Data regarding girls under age 21 years presenting with POI during the years 2000-2016 were collected from all the pediatric endocrine units (14 centers). Iatrogenic cases were excluded. The incidence rate of new POI cases was calculated based on birthrate information from the Israeli Central Bureau of Statistics.

Results: 113 girls met the criteria of POI. The distribution of etiologies was: Turner syndrome/mosaicism in 49/113 (43%), idiopathic in 36/113 (32%) and other (genetic, autoimmune, etc.) in 28/113 (25%). During the years 2009-2016 compared to 2000-2008, the incidence rate of new POI diagnoses per 100,000 births doubled (3.8 versus 1.8, P=0.0003), and incidence rates of both idiopathic and other etiologies tripled (P=0.003 and 0.01 respectively). In contrast, the incidence of Turner syndrome was constant (P=0.3). In the

age group of 15-21 years, the current incidence of non-Turner POI in adolescents is 1 per 100,000 person-years.

Conclusions: The current study was the largest scale multi-center study in adolescents and a significant increase in the rate of POI was observed over the last decade, among non-Turner cases. The contribution of environmental and epigenetic factors to this remarkable increase should be studied.

Estrogen Suppresses Left Ventricular Pro-fibrotic Gene Expression via Up-regulation of miR-26a, 133a, 34a in Ovariectomized Mice

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Introduction: Menopause is associated with increased cardiovascular morbidity and mortality. The incidence of heart failure with preserved ejection fraction (HFpEF) is higher in women, and occurs most commonly after menopause. HFpEF is characterized by cardiac remodeling, myocardial stiffness and diastolic dysfunction. We previously found that estrogen suppresses the expression of fibrosis markers in the left ventricle (LV) of ovariectomized (OVX) mice. Dysregulation of micro-RNAs (miRNAs) has been reported to influence cardiac fibrosis markers.

Aim: To test whether estradiol modulates gene expression of cardiac remodeling markers by regulating fibrosis-related miRNAs in the LV of 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 sc 17-β-estradiol (E2) (10μg/kg) or a vehicle was then administered for 6 weeks to OVX mice. Upon sacrifice mRNA was extracted from the LV. miRNA-specific cDNA was generated. Relative miRNA expression was determined by the comparative CT method and normalized to *U6.*

Results: E2 administration dramatically reduced mRNA expression of the fibrosis markers: *Col1α1*, *Col3α1, TIMP1*, *TGFβ1* in OVX mice. Strikingly, E2 significantly increased the expression of fibrosis-down regulating miRNAs: miR-26a (1.7-fold, *P*0.01), miR-34a (2-fold, *P*0.01) and miR-133a (1.7-fold, *P*0.05) previously shown to inhibit *Col1α1* and *TGFβ1* mRNA expression.

Conclusions: E2 increases the expression of the fibrosis down-regulating miRNAs: miR-26a, miR-34, miR-133a, suggesting a possible mechanism by which E2 inhibits mRNA expression of fibrosis-related proteins. This maybe an additional pathway by which estrogen exerts its cardio-protective effects in postmenopausal women.

Obesity, Metabolic Syndrome (Sunday, April 7, 2019 08:30)

Revisiting the Normal Body Mass Index among Ethiopian Adolescents: A Nationwide Study of 317,000 Males and Females.

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Aims: Shifts in populations have drastically increased cardiovascular risk factors and disease rates. We assessed the association between body mass index (BMI) and blood pressure (BP) levels among adolescents of Ethiopian origin and their secular trend of overweight and obesity.

Methods: The study cohort comprised of adolescents aged 16-19 years, who were medically examined prior to military service between 1992 through 2016. Participants of Ethiopian origin were classified into Israeli-born (N=15,793) and immigrants (N=23,487), and adolescents from families that are at least 3 generations in Israel served as controls (n=277,789). BMI was stratified by sex and divided to 6 groups:17, 17.5-18.4, 18.5-19.9, 20.0-22.4, 22.5-24.9, 25.0 kg/m^2. Hypertensive-range BP values adjusted for age, sex and height served as outcome.

Results: The occurrence of hypertensive-range measurements increased with the length of residency in Israel: 7.3%, 10.6% and 14.4% in males who immigrated at ages 12-19, 6-12 and 0-6 years respectively, and 11.5%, 16.7% and 19.3% among females, respectively. Israeli- born Ethiopians had significantly higher risk for hypertensive range measurements at any given BMI 20 kg/m^2 compared to controls, after accounting for socio-demographic variables and medical history. Between 1992 and 2016, there was a 10-fold and 5-fold increase in overweight and obesity in males and females of Ethiopian origin respectively, compared to a 2-fold increase in the controls.

Conclusions: The association between abnormal BP and BMI is significantly steeper among Israelis of Ethiopian origin. This population requires targeted surveillance and appropriate intervention given the dramatic increase in obesity, especially among females.

Severe Obesity and Cardiometabolic Comorbidities in Adolescents: Chronology of an epidemic

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Aims: To assess the trend in the prevalence of severe obesity in a national population of adolescents and to evaluate the association of severe obesity with major cardio-metabolic morbidities.

Methods: The prevalence and severity of obesity was determined among 373,226 Israeli adolescents with abnormal BMI (≥85th percentile for age and sex) examined in an obligatory health assessment at mean age 17.3±0.5 years between 1967 and 2015. Data on abnormal blood pressure measurements and type 2 diabetes (T2DM) were considered in a subgroup of 230,639 adolescents examined from 1997 through 2015. Participants were classified into overweight (≥85th to95th percentile), class I obesity (≥95th percentile to 120% of the 95th percentile), class II obesity (≥120% to 140% of the 95th percentile), and class III obesity (≥140% of the 95th percentile).

Results: There were an approximately 2, 4, 16 and 45 fold increases in the prevalence of overweight and class I, II, and III obesity, respectively, between the late 1960's and 2013-2015, with an accelerated increase in class II and III obesity during the last two decades. Compared to the overweight adolescents, the odds ratios (OR) for hypertension in the class I, II and III obesity groups respectively were 1.4, 2.1, and 2.9 in males, and 1.8, 2.6 and 3.4 in females. The OR for T2DM increased markedly in class I, II and III obesity compared to the overweight groups, from 5.6 to 38 fold in males and from 4.7 to 25 fold in females.

Conclusion: The increase in the prevalence of obesity was differential and was more pronounced for all classes of severe obesity. This steep increase in the odds for hypertension and particularly T2DM along the obesity classes suggests that the burden of cardio-metabolic morbidities is expected to increase

Epigenetic-changes in Response to Metabolic Modifiers in late-life: Exercise, High Fat Diet and Angiotenin1-7 Effects on Metabolic Health and DNA Methylation in Frail Old Mice

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Background: Reduced muscle and bone mass and quality are seen in both aging and the metabolic syndrome (MetS). We showed that exercise and Angiotensin1-7 (A1-7) can ameliorate this burden in young mice, but their effect vis-a-vis aging is unknown.

Aims: To assess the effects of exercise under normal and high-fat diet (HFD) with or without A1-7 on bone and muscle in aged mice.

Methods: 19-months-old-mice receiving HFD or normal-chow (NC) with or without 3-months exercise (treadmill, 6 days/week, 20 min/day or A1-7 (alzet-pumps; 0.6 mcg/kg/d). Bone was evaluated by microCT. Global quantification of the epigenetic modification 5-methyl-cytosine (5mC) by LC-MS/MS in white adipose tissue (WAT) and Gastrocnemius muscle.

Results: Old, sedentary mice were metabolically "starved" with low serum glucose and triglyceride. (A) Exercise *per se* rehabilitated glucose, triglycerides levels and muscle quality (enhanced muscle-fiber sectional area), accompanied by reduction in muscle 5mC levels (p0.05) (B) Combination of exercise with A1-7 improved bone geometry and density in NC mice but not during HFD. Combination of A1-7 and exercise led to a reduction in global 5mC levels both in the gastrocnemius muscle and in WAT (p0.05), thus suggesting that some of the effects maybe induced by changes in methylation patterns.

Conclusions: The beneficial effects of A1-7 and exercise in aging skeletal tissue are operative only in NC but not in the presence of HFD. These beneficial effects are accompanied, and indeed, may be partly mediated by reversal of gene silencing as depicted by lesser DNA methylation in skeletal muscle.

Obesity, Metabolic Syndrome (Sunday, April 7, 2019 08:30)

Circulating Endocannabinoids are Reduced following Bariatric Surgery and Associated with Improved Metabolic Homeostasis in Humans

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Introduction: The prevalence of obesity and its associated metabolic disorders nearly tripled in past four decades. The endocannabinoid (eCB) system plays a crucial role in the development of obesity. Higher circulating eCB levels found to be positively correlated with obesity and related comorbidities. However, there is limited information regarding the association of circulating eCBs with the metabolic improvement following bariatric surgery, which is the most effective option in terms of weight loss and metabolic improvements for morbidly obese patients.

Aim: To assess the levels of circulating eCB and the association between their levels and various metabolic features pre- and post-operatively.

Methods: By using liquid chromatography-mass spectrometry we measured the levels of circulating eCBs and their related molecules and assessed various metabolic parameters in 65 morbidly obese patients before and one year after a laparoscopic sleeve gastrectomy (LSG) surgery.

Results: Levels of 2-arachidonoylglycerol (2-AG), anandamide (AEA), and arachidonic acid (AA) were reduced post operatively with no differences in serum oleoylethanolamide (OEA) levels. Positive correlations were found between delta AA and waist circumference, free fat mass, SteatoTest score and alanine transaminase. Delta AEA levels positively correlated with weight circumference, whereas delta 2-AG levels positively correlated with total cholesterol, triglycerides and steatoscore.

Conclusions: LSG surgery induces reductions in circulating eCBs, and these changes are correlated with clinical benefits related to the surgery. These findings also support the notion that therapeutic strategies aiming to decrease eCB `tone` in obese individuals may provide a clinically relevant tool to combat the obesity epidemic worldwide.

Abdominal Obesity as a Continuum: What is a Normal Waist Circumference in Israel?

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Introduction: For the definition of the abdominal obesity and the metabolic syndrome (MS), different normalcy cut-off levels for waist circumference (WC) are now applied in the US vs. Europe (M/F-102/88 cm; 94/80 cm, respectively). In Israel 57% of the population aged 65yrs or more have increased WC by the US criteria.

Aim: To explore "normalcy" of WC in relation to metabolic health in Israel

Methods: We examined the relation between WC, metabolic health and age in a large sample of 19,328 subjects in a health screening program at The Tel Aviv-Sourasky Medical Center. Normal metabolic state was defined by ATPIII criteria

Results: 1) Even subjects at the lowest WC range had a sizable rate of some cardiometabolic derangement (M/F:25%/18%). 2) With increasing WC from 70/65 cm (M/F) and higher, the fraction of subjects free of any MS components declined linearly in both sexes. At WC of 95cm (just above the European cutoff) 55% of men already showed at least one metabolic anomaly and as did 40% of women with WC of 80 cm. 3) The fraction of metabolic derangement-free subjects declined linearly with age, in subjects with either normal (94cm) or increased WC.

Conclusion: 1) WC is a continuous cardiometabolic risk factor, starting as of the leanest range. 2) The European criteria for normal WC are more suitable for Israel than the US-defined cutoff levels and should replace the currently used US WC. 3) The lean group with some MS component (~20%) merits special future research.

Obesity, Metabolic Syndrome (Sunday, April 7, 2019 08:30)

Therapeutic Efficacy of an Indoline Derivative in Preventing the Development of the Metabolic Syndrome

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Introduction: Despite emerging strategies and search for new remedies, no current single treatment has been able to reverse or at least stop the progression of the metabolic syndrome. AN1284 is a novel indoline derivative, which has been shown to have anti-oxidant and anti-inflammatory activities in several pre-clinical models.

Aim: To examine the therapeutic potential of AN1284 in ameliorating the development of the metabolic syndrome and its comorbidities in a mouse model for type-2 diabetes.

Methods: Obese and diabetic BSK-*db/db* mice were chronically treated with AN1284 (2.5 or 5 mg/kg, SC) via osmotic mini-pumps for 3 months and were compared to vehicle-treated obese and lean controls. Various metabolic parameters were measured, including body weight and composition, glucose homeostasis, liver and kidney function, and a full metabolic analysis was made.

Results: Chronic treatment with AN1284 resulted in increased utilization of body fat toward energy, leading to weight loss and decreased body fat mass. AN1284 prevented the upregulation in insulin levels and preserved β cell mass, possibly indicating a higher insulin sensitivity. Improved hepatic steatosis, assessed by measuring liver triglycerides and circulating transaminases, as well as preserved kidney function, determined by histology and biochemistry analyses of albumin and creatinine, were found in mice treated with AN1284 in the two doses tested.

Conclusions: Our findings demonstrate that in a mouse model for the metabolic syndrome, AN1284 has a potential to prevent the development of many of the complications associated with the metabolic syndrome, suggesting that further preclinical evaluation of this drug should be considered.

Higher Insulin Degrading Enzyme levels In Subjects with the Metabolic Syndrome

Yael Sofer[1], Yuval Nash[2], Itai Benhar[3], Ofir Forsht[2], Esther Osher[1], Limor Nahary[2], Sigal Shaklai[1], Karen Torjman[1], Merav Serebro[1], Elia-Belle Touati[1], Michal Yacobi Bach[1], Yonit Marcus[1], Brurya Tal[1], Jessica Sack[1], Gabi Shefer[1], Nathan Landis[1], Naftali Stern[1], Dan Frenkel[2]

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Background

With the growing prevalence of obesity, there is also a rise in the incidence of metabolic syndrome (MS). It is characterizes by hyperinsulinemia, increased fasting glucose, hypertriglyceridemia, low HDL, increased waist circumference and hypertension.

Insulin-degrading enzyme (IDE) is the major enzyme responsible for insulin degradation among other proteins linked to glucose metabolism such as glucagon. Using genome wide associated studies, IDE was identified as a diabetes susceptibility gene. Furthermore, inhibition of IDE was suggested as therapeutic target for type 2 diabetes.

Objectives

Study the difference in IDE levels between healthy and MetS subjects. Characterize metabolic parameters which correlate with IDE.

Explore IDE levels in a mouse model of obesity/ insulin resistance.

Methods

We developed highly specific anti IDE antibodies with the ability to detect human IDE levels using ELISA. IDE levels were measured in 51 MS subjects and 24 controls.

Results

As expected, MS subjects had higher BMI, glucose, triglycerides and insulin levels, with lower HDL levels. IDE levels were higher in MS subjects(mean 765.46 +/-734.56 vs 441.22 +/- 142.77 pg/microliter; $p<0.05$) . We also found a strong correlation between IDE levels and triglyceride levels ($r= 0.368$; $p<0.05$), insulin ($r=0.331$, $p=0.01$), c-peptide ($r=0.661$, $p<0.05$), and negative correlation with HDL levels ($r= -0.301$; $p=0.05$). Of interest, IDE levels in MS subjects were clearly segregated into two different subgroups, subjects with "normal IDE", with value distribution and mean(n=26; 278.16+/-156.66 pg/ul) which were indistinguishable from the normal control group and subjects with high IDE (n=25; 1272.26+/-757.47 pg/ul, p

The low IDE MS group was older (54 +/- 10 vs 45+/-13 years; $p=0.01$) and had higher glucose levels than the normal IDE MS group (94+/-20 vs 80+/-8 mg/dl; $p=0.01$).

Conclusions

IDE is higher in MS subjects and is related to age and fasting glucose. Whether or not this is a compensatory mechanism or contributes to disease progression remains to be explored.

Symposia 1: CAH (Sunday, April 7, 2019 14:00)

Genotype DOES Predict Phenotype in CAH Secondary to 21 -Hydroxylase Deficiency- The Israel Experience

Naomi Weintrob, **Naomi Weintrob**[1], David Zangen[2]
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Since 1995, Dr. Shoshana Israel, at Hadassah Hospital, developed the molecular screening core for analyzing the *CYP21A2* gene in patients with the clinical and biochemical diagnosis of 21 hydroxylase deficiency (21OHD). The screening used mainly PCR and Sequence specific oligo probe hybridization. Later on also direct sequencing of exons 4-10 when the 9 most common disease causing biallelic changes were not detected in the initial analysis or when genotype did not fit phenotype.

Naama Ayalon (MD thesis) aimed here to characterize: 1. the prevalence of various *CYP21A2* gene mutations among subjects with 21OHD in Israel. 2. The ethnic distribution of specific mutations. 3. The Genotype-phenotype correlations. The study was retrospective and data was collected consecutively from the subjects` files kept in an alphabetical order in the lab. The ethnic origins were classifed into five groups: Arab, Yemenite / Ethiopian, Sephardic, Ashkenazi and Middle Eastern Jews. The genotypes were classified into three groups according to the residual reported enzyme activity for each mutation, severe, moderate and mild.

Results

Our cohort included 798 families with 1,526 subjects. Only the first subject of each family was considered for statistical evaluation. Males were referred much more frequently than males (659 vs131). Only 429 (54%) out of 798 had a diagnosis of CAH: 366 had non-classic (NCCAH), 17 SV and 46 SW. The most common mutation detected was the mild mutation V281L (70% of alleles). The frequency of the other mutations by decreasing order was as follows: I2Splice - 11%, Q318X - 5.5%, normal allele - 5.1%, I172N - 3.5%, P30L - 2.3% and Deletion - 1.3%. Other mutations were found in less than 1% of alleles. The prevalence of the different mutations was specific for different ethnic origin (632 participants). The V281L mutation was found in 100% and 61.1% of Ethiopian and Ashkenazi Jews respectively but only in 42.9%, 30%, 10% in Sephardic, Middle East and Yemenite Jews respectively, and in 25% of the Arabs. The I2Splice mutation was more frequent (11.2%) among Arabs, compared with the 6.6% found in the entire cohort. Q318X was detected more commonly (8.6%) among the Sephardic Jews, and among the Arab (7.3%), as opposed to 4.9% in the general population. The frequency of the P30L mutation was relatively high among Yemenite Jews, 9.5%, compared to the 0.9% in the entire CAH group. In 42 alleles, (5.7%) no mutation was found

In 379/ 427 patients, 88%, the genotype matched the phenotype. In 40 patients only one mutated allele was found and in the other 8 subjects with two known mutations the genotype did not match phenotype. The positive predictive value (PPV) for phenotype genotype correlation for all patients with 2 mutations was 98%: 90% for the very severe mutations group, 92% for the group of severe mutations and 99% for the mild mutations group. These results support the current screening method of 9 mutations by PCR. This finding is similar to previous studies performed in other world populations.

One limitation of this study is the relatively small number of classic 21OHD. Since the importance of genetic and prenatal counseling is far more important in the classical forms, a larger sample of classical patients` need to be examined to further delineate origin-mutation and genotype-phenotype associations.

A by-product finding of this survey was that many subjects (34.5%) were sent for genetic testing without biochemical proof of CAH diagnosis and therefore no mutations were found. This finding support the implantation of stringent criteria for sending patients for molecular analysis of the CYP21A2 gene.

21-Hydroxylase Deficiency, Insights from the Molecular Lab and Implication for the Clinic

Adi Mory
Genetic Laboratory, Rambam Health Care Campus

Background: 21-hydroxylase deficiency (21-OHD) is the most common cause of congenital adrenal hyperplasia (CAH). Identification of bi-allelic pathogenic variants in *CYP21A2* confirms the diagnosis and allows for patient management and segregation analysis.

Methods: Since May 2018, the genetic diagnosis of 21-OHD in Israel has been performed in the molecular lab at the Rambam Genetics Institute, applying new testing methodologies, mainly Sanger sequencing and MLPA, which allows the diagnosis of large deletions and duplications.

Results: About 250 individuals were referred for 21-OHD testing (July 2018-Feb 2019). The clinical indications consisted of classic or non-classic CAH, family segregation and spouse testing. Of the 135 patients with suspected non-classic CAH, 47% were diagnosed with bi-allelic mutations confirming the diagnosis. Bi-allelic mutations were found in 9 out of 10 classic CAH patients, including complete or partial deletion, and 3 unique mutations. Of note, the Q318X mutation was observed in 15 individuals (6%); however, in 10 cases a duplicated allele was observed (66%) indicative of the Q318Xdup variant.

Discussion: Genetic diagnosis was established in all classic CAH patients, but one who was diagnosed over 40 years ago, questioning his diagnosis. In non-classic CAH, only 47% patients were found to have bi-allelic mutations, while 28% were mutation-negative. There should be further discussion as to the necessity of genetic testing in couples when one is homozygous for the V281L mutation, as their offspring are at risk for non-classic CAH only, and might not be the target population for prenatal diagnosis in general, and for PGD in particular.

Bone Metabolism (Monday, April 8, 2019 08:00)

Denosumab-induced Hypocalcemia in Patients with Osteoporosis- Can You Know Who Will Get Low? Retrospective Analysis of Real-world Data

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Introduction: Hypocalcemia was reported at an incidence of 0.05-1.7% in randomized controlled trials of the efficacy of denosumab in postmenopausal women. Long-term real-life data is lacking.

Aim: To assess denosumab-induced hypocalcemia in a large cohort treated for two years.

Methods: Retrospective analysis of medical records of osteoporosis patients treated with denosumab in January 2010 to August 2018 at Clalit Health Services, Dan-Petah-Tikva district.

Results: Of 2,005 patients (93% women) aged 76±9 years (mean±SD) treated with denosumab for median duration of 2.5 years, 149 (7.4%) developed hypocalcemia on therapy: 66 patients after 0.5-1 year, 48 after 1-2 years and 35 after 2 years.

Males, pretreatment albumin-adjusted calcium level and creatinine level (11% vs. 6%, 9.1±0.4 vs. 9.4±0.5mg/dL, 0.9±0.5 vs. 0.8±0.3mg/dL, p0.05, hypocalcemic vs. normocalcemic subjects, respectively) were associated with risk of hypocalcemia.

Age, body mass index, pretreatment levels of 25-dihydroxyvitamin D, parathyroid hormone and alkaline phosphatase were similar in normocalcemic and hypocalcemic cases and did not predict the development of hypocalcemia.

The rate of hypocalcemia increased in parallel to a decrease in eGFR (p=0.078 for difference between eGFR ranges).

Baseline calcium level ≤9.31mg/dL predicted hypocalcemia with a sensitivity of 77% and specificity of 56%.

Conclusion: Real-life rates of denosumab-induced hypocalcemia are higher than previously shown. Hypocalcemia might develop during up to 2 years of ongoing treatment. Serum calcium monitoring is especially required in high risk subgroups: males, subjects with kidney dysfunction and pretreatment calcium lower than 9.31mg/dL.

Magel2 Modulates Bone Remodeling and Mass in Prader Willi Syndrome by Affecting Oleoyl Serine Levels and Activity

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Background: Among a multitude of hormonal and metabolic complications, individuals with Prader-Willi syndrome (PWS) exhibit significant bone abnormalities, including decreased bone mineral density, osteoporosis, and subsequent increased fracture risk.

Aim: To identify the molecular contributors to the development of PWS-induced bone disorders.

Methods: Skeletal characterization was performed utilizing combined µCT/histomorphometric analysis, serum markers of bone turnover, and 3-point bending test. *N*-Oleoyl serine (OS) levels were determined by LC-MS/MS quantification.

Results: Here we show in mice that loss of *Magel2*, a maternally imprinted gene in the PWS critical region, resulted in reduced bone mass, density, and strength, corresponding to that observed in humans with PWS as well as in individuals suffering from Schaaf-Yang syndrome (SYS), a genetic disorder caused by a disruption of the *MAGEL2* gene. The low bone mass phenotype in *Magel2*$^{-/-}$ mice was attributed to reduced bone formation rate due trans-differentiation of osteoblasts-to-adipocytes, as well as, significantly increased osteoclastogenesis and osteoclast activity. The absence of *Magel2* in humans and mice resulted in reduction in the fatty acid amide bone homeostasis regulator, OS, whose levels were positively associated with osteoblast activity and bone mineral density in humans and mice. Full attenuation of the skeletal abnormalities in *Magel2*$^{-/-}$ mice was achieved with chronic administration of a novel synthetic derivative of OS.

Conclusions: *Magel2* plays a key role in modulating bone remodeling and mass in PWS by affecting OS levels and activity. The use of potent synthetic analogs of OS should be further tested clinically as bone therapeutics for treating bone loss.

Bone Metabolism (Monday, April 8, 2019 08:00)

Sex-specific Regulation of Bone Resorption in the Osteoclast Lineage by Krox20: Hormone-independent Sexual Dimorphism

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Krox20/EGR2 is a zinc finger transcription factor, implicated in the development of the hindbrain, nerve myelination, and tumor suppression. We reported that systemically *Krox20*-haploinsufficient mice have a low bone mass with increased bone resorption, demonstrating that *Krox20* also regulates adult bone metabolism. Using MicroCT and histomorphometry, we now show that this phenotype is restricted to females. In addition, we discovered that conditional knockout of *Krox20* (cKO) restricted to osteoclasts progenitors induce the same female-specific bone loss observed in systemic mutants. To elucidate the mechanism of this sexual dimorphism, we examined *in vitro* the sex- and hormone-dependent effects of *Krox20* deficiency on proliferation (using MTT assay) and apoptosis (using Annexin V) of osteoclastic cells. Our results indicate that male and female sex hormones (dihydrotestosterone - DHT and estradiol - E2, respectively) as well as *Krox20,* inhibit preosteoclast proliferation and augment osteoclast apoptosis. However, *Krox20* expression was inhibited by DHT and E2, negating the hypothesis that the effect of sex hormones is mediated by increasing *Krox20* expression. Interestingly, the effect of *Krox20* deficiency was seen only with cells derived from female animals, regardless of the sex hormones added *in vitro*. In addition, the expression of several *Krox20*-related genes, including NAB2, demonstrated a sexual dimorphism between male- and female-derived cultures. This sex-specific epigenetic profile was established at puberty, maintained in the absence of sex hormones, and explains the female-specific skeletal importance of *Krox20*. These findings emphasize the medical importance of sex differences, which may be determined at the epigenetic level.

Bone Metabolism (Monday, April 8, 2019 08:00)

The Association between Glycemic Control and Hip Fracture Risk- A Retrospective Cohort Study

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Introduction

Fragility fractures are increasingly recognized as a complication of diabetes mellitus (DM). Disease duration, poor glycemic control, diabetes complication, and glycemic variability may be associated with increased risk.

Aim

To investigate the association between glycemic control and hip fracture (HF) risk in a cohort of diabetic patients.

Methods

This retrospective cohort study included all patients aged 50 years and older with diagnosis of DM or HbA1c measurement ≥6.5% between 2001-2016, from the Southern region of Israel, and who were registered with Clalit Health Services. Patients were followed up to January 2018 for the primary outcome- HF. Association between mean HbA1c in the last year of follow-up and HF risk was analyzed using logistic regression.

Results

Our cohort consisted of 51381 diabetic patients (47% males), of whom 1377 (2.67% [69% females]) experienced HF during the observation period. A positive association between HF risk and elevated HbA1c values was demonstrated. Multivariate analysis adjusted for gender, age, charlson index, duration of diabetes and glycemic variability (as coefficient of variation) showed that the adjusted odds ratio (OR) for HF was 0.390 (0.309-0.491) for HbA1c6.5%, 1.685 (1.389-2.044) for 7.5%≤HbA1c8.5%, 2.765 (2.208-3.462) for 8.5%≤HbA1c9.5%, and 9.19 (7.507-11.25) for HbA1c≥9.5% (p

Conclusion

Worse glycemic control was exponentially associated with an increased HF risk.

The Impact of Diabetes Mellitus on Survival after Hip fracture a Single Center Experience

Vitaly Medvedovsky[1], Roni Gat[2], Uri Yoel[1], Lior Baraf[1], Dayana Cohen[1], Tamar Eshkoli[1], Victor Novack[2], Ethel Siris[3], Merav Fraenkel[1]

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Background

Diabetes mellitus (DM) is a risk factor for osteoporotic fractures, possibly associated with increased mortality rate following fracture.

Aim

To assess the association between DM status and all-cause mortality risk following hip fractures (HF).

Methods

Patients insured by Clalit Health Service over age 50 admitted to Soroka University Medical Center with HF (ICD-9 820) between the years 2012-2018 were included. DM was diagnosed according to one of the following: HbA1C6.5%, ICD-9 code 250, purchase of antidiabetic drugs or random glucose level 200mg/dl prior to HF. Demographic data, co-morbidity, drug purchase and laboratory data were collected from the electronic medical records.

Results

Two thousand eight hundred and forty HF patients were included; 40% were diagnosed with DM prior to HF. Mean age and sex were similar in both groups (78.6 and 66.4%). At last follow up death occurred in 45.1% of patients with DM and in 37.7% without DM (p0.009). Cox regression adjusted for age, sex and co-morbidities (malignancies, lung diseases, CHF, CKD, Dementia, PVD, liver disease) showed significant increase in risk of death after HF in patients with DM compared with non-diabetic patients (HR 1.26, p0.001), while with adjustment only for Charlson index statistical significance was lost. Assessment of survival according to bands of mean A1c in the 2 years before HF showed a trend for worse outcome with higher A1c that did not reach statistical significance.

Conclusions

DM patients have a 26% increased post hip fracture mortality compared to non-diabetics. Part of this increased risk is due to higher burden of chronic disease.

Trabecular Bone Score (TBS) Change is Not Predicted by Bone Turnover

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Introduction:

Bone mineral density (BMD) measurement by Dual-energy x-ray absorptiometry (DXA) is the mainstay of osteoporosis diagnosis, despite its known caveats. TBS evaluates the microarchitecture of vertebrae and aids in fracture risk assessment. While longitudinal change in BMD is a well-recognized tool for patient`s follow-up, the significance of change in TBS over time is yet to be established.

Aim:

To examine the association between change in TBS, BMD, clinical parameters, medication exposure and bone resorption marker (CTX).

Methods:

Examinees with two consecutive DXA results were located using our center BMD-TBS database. Patients with a detailed electronic medical record (EMR) in our tertiary osteoporosis service were included. Information on comorbidities, medications, fractures and CTX was extracted from EMRs.

Results:

Of 700 patients with two DXA results, 110 had detailed EMR. The mean age was 67±10 and majority were female. TBS change was significant (over 5%) in 38(34.5%). BMD increased in 79(71.8%) and decreased in 31(28.2%). While CTX was significantly higher in patients with BMD loss (398 vs 281 pg/ml, p0.05), no correlation was observed between CTX and TBS change. Patients with TBS gain were older, 72±6 vs 64±6, p

Conclusions: A strong association was observed between bone resorption and BMD, but not TBS, change. The significance of longitudinal dynamics in TBS, its clinical interpretation and interrelation with medications used to treat osteoporosis, warrants further evaluation.

Low Trabecular Bone Score with or without Osteoporosis is Differentially Linked to Distinct Clinical Conditions.

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

Introduction: Trabecular bone score (TBS) is a bone texture index derived from lumbar spine dual-energy x-ray absorptiometry (DXA) images.

Aim: To assess which medical conditions are associated with low TBS.

Subjects and methods: A cross sectional study conducted in the bone clinic at the Tel-Aviv-Sourasky medical center. BMD was measured by DXA (Lunar Prodigy Primo) and TBS was measured from DXA L1L4. We collected demographic and clinical data from the medical files. To be included in this analysis, subjects had to present with a L1L4 TBS adjusted T-Score (aTBS) -3.

Results: We identified 110 subjects (F/M=109:1) whose aTBS was3, of whom half had osteoporosis by BMD and half were normal/osteopenic. Mean age was 68±12 and mean BMI 28.3± 5.8kg/m2. The group with low aTBS without osteoporosis had significantly higher rates of obesity (52% vs 17%, P0.01) and diabetes (36% vs 17%, p=0.003). In contrast, the group with low aTBS and osteoporosis included a higher rate of subjects with inflammatory diseases (15.6% vs 3.6%, p=0.035), chronic steroid treatment (22% vs 8%, p0.01) and cancer [papillary thyroid carcinoma (8% vs 0%, p=0.025); breast cancer cases (16% vs 12%, NS); overall rate of cancer (29% vs. 14%; p=0.075)].

Conclusion: In our study population, low TBS is significantly linked to distinct medical conditions, in relation to the presence or absence of osteoporosis. Low TBS associated with low BMD segregated with the presence of inflammatory diseases, chronic steroid treatment, and cancer whereas low TBS with normal/osteopenic BMD was associated with obesity and diabetes.

Diabetes, Basic and Clinical (Monday, April 8, 2019 08:00)

Parenteral Cephalosporins and Parenteral Glucose During the Neonatal Period are Associated with Pediatric Type 1 Diabetes Development

Iren Zargari[1,2], Adi Adar[1,2], Rimona Keidar[2,3], Ori Eyal[3,4], Neta Loewenthal[5], Orit Pinhas-Hamiel[2,6], Iris Morag[2,7], Milana Levy[8], Orna Dally-Gottfried[9], Zohar Landau[2,10], Floris Levy-Khademi[11,12], David Zangen[11,13], Smadar Eventov-Friedman[11,14], Ilan Youngster[2,15], Marianna Rachmiel[1,2]

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Background: The incidence of type 1 diabetes (T1D) increases worldwide. Prematurity is not a risk factor for T1D, however, preterm population is meticulously monitored during hospitalization.

Aim: to assess the association between nutritional, antibiotic and parenteral exposures during the neonatal period and pediatric T1D.

Methods: a multicenter, paired case-control study. Preterm subjects who developed T1D before the age of 18 years (T1D group) were paired with subjects who didn`t develop TID (Control group) by: gender, gestational age (GA), month and birth medical center. Data included delivery mode, ethnicity, weight, hospitalization length, medications, parenteral fluid, feeding modes and timing. Multivariate analysis via Generalized Estimating Equations using a binary logistic regression model was performed

Results: T1D group included 52 subjects, 26 males, median GA 35 (26-36), mean BW 2307.6±534.5. Control group included 132 subjects, 67 males, median GA 35 (27-36), mean BW 2094.5±484.1. Multivariate analysis revealed significant association between treatment with cephalosporins beyond the first week of life, later day of parenteral glucose initiation and oral feeding during the first week of life and the development of pediatric T1D (OR 5.593, 95%CI 1.55-20.07, p 0.008 and OR 1.61, 95%CI 1.06-2.45, p 0.025, OR 3.029, 95%CI 1.18-7.76, p 0.021, respectively).

Conclusions: This is the first report indicating an association between exposure and timing of antibiotics, oral feeding and parenteral glucose during the neonatal period with T1D. This indicates the need for a larger study in a term population to conclude clinical implications of exposure to these substances during the neonatal period.

Endoplasmic Reticulum (ER) Stress Inhibits Insulin/IGF-1 Signaling in β-cells and Hepatocytes by Reducing P85α Expression

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Introduction: ER-stress plays an important role in the pathophysiology of diabetes. We have recently shown that early in life ER-stress reduces β-cell growth and function in the *Akita* mouse, which carries a mutation in the proinsulin gene causing severe neonatal diabetes. This resulted from inhibition of AKT-mTORC1 signaling in β-cells; however, the mechanisms involved are unknown.

Aim: To investigate how different types of stress, including proinsulin misfolding, pharmacological inducers of ER stress and fast, affect Akt-mTORC1 signaling, focusing on the expression and intracellular localization of P85α, the regulatory subunit of PI3-kinase.

Methods: P85α expression, AKT and mTORC1 activities were analyzed in neonate *Akita*-islets and INS-1E β-cells treated for 48h with low-dose thapsigargin or tunicamycin by immunostaining and Western blotting for P85a, p110, $pAkt^{Ser473}$, $pAkt^{Thr308}$ and $pS6^{Ser240/244}$.

Results: P85α protein level was decreased and the AKT-mTORC1 signaling inhibited in neonate *Akita* islets and in INS-1E β-cells treated with thapsigargin and tunicamycin. Moreover, thapsigargin increased the nuclear localization of p85α without affecting its mRNA level and protein stability. Overnight fasting of WT-mice decreased hepatic expression of P85α and AKT-mTORC1 signaling and increased the phosphorylation of eIF2α, a repressor of protein synthesis under fast and ER stress.

Conclusions: β-cells and hepatocytes develop insulin resistance in response to metabolic and ER-stress by inhibiting P85α expression and intra-cellular localization, probably *via* eIF2α, which inhibits protein synthesis. These findings provide new insight on the regulation of insulin signaling by ER-stress and fast; this has important implications for glucose homeostasis in physiology and in diabetes.

Pediatric Type 1 Diabetes Mellitus Incidence rate and Socioeconomic Ranking in Israel

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[2]*(emeritus), Geological survey of Israel, 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 risk factors. Studies searching for association between socioeconomic ranking and Diabetes Mellitus showed negative correlation between socioeconomic ranking and type 2 Diabetes Mellitus (T2DM) which was not found in T1DM.

Aim: To assess possible correlation of pediatric T1DM incidence rates in settlements in Israel and socioeconomic ranking.

Methods: In a 4 years retrospective population study pediatric T1DM incidence rates were calculated for the period 2012-2015 in 74 municipalities with population above 5000 and various socioeconomic ranking in Israel, based on data obtained from the national T1DM registry and the Israeli Central Bureau of Statistics.

Results: During the years 2012-2015 a total of 1126 subjects age 0-18 years with newly diagnosed T1DM from 74 municipalities with population above 5000 in Israel were reported by the Israeli National T1DM registry. In order to assess possible correlation between socio-economic ranking (index value) and T1DM incidence rate, the diabetes incidence rate was displayed according to localities using linear regression. There was a significant association between the index value and the incidence rate of T1DM (β=-1.392 p=0.036), so the lower the socioeconomic ranking, the higher incidence of T1DM.

Conclusions: The results may imply that lower socioeconomic ranking may contribute to the rising incidence of pediatric T1DM in Israel. As this contradicts previous studies including the hygiene theory further research is mandatory.

Why Should We Measure Low Density Lipoprotein Cholesterol Directly? Comparison between Plasma LDL-Cholesterol Assessment by Friedewald Equation and Direct Measurement

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INTORDUCTION: LDL cholesterol (LDL-C) is an important biomarker for atherosclerotic cardiovascular disease. In clinical and research settings worldwide, levels of LDL-C are not directly measured but are estimated by the Friedewald equation: LDL-C = Total cholesterol – HDL cholesterol – (Triglycerides/5). The inaccuracy of indirect assessment of LDL-C by the equation can be overcome by direct measurement of LDL-C.

AIMS: To compare the accuracy of calculated vs. directly measured plasma LDL-C, and evaluate potential measurement bias.

METHODS: Lipid profiles with triglycerides (TG) 400 mg/dl were obtained from patients at the Chaim Sheba Medical Center - a heterogonous population of patients. Plasma LDL-C concentrations were directly measured (dirLDL-C) and correspondingly calculated by the Friedewald equation (calcLDL-C).

RESULTS: 32,245 samples were analyzed. In most subjects, the Friedewald equation underestimated LDL-C concertation. In 7,693 samples (24%), the difference between dirLDL and calcLDL exceeded 20 mg/dl. The difference between dirLDL and calcLDL correlated to TG levels, including TG levels within the normal range. A discrepancy between dirLDL and calcLDL was also observed at relatively low total cholesterol. Additional evaluation showed a direct correlation between the dirLDL levels and apolipoprotein B levels.

CONCLUSIONS: In the current era of extremely low plasma LDL-C treatment goals, and availability of potent lipid lowering medications, accurate determination of plasma lipids is crucial. Direct measurement of LDL-C is more precise than LDL-C estimation and overcomes inaccuracies due to elevated TG levels or low LDL-C levels. Direct measurement of plasma LDL-C is favorable over calculating LDL-C levels, and therefore advocated.

SGLT2 Inhibition Ameliorates Diabetic Nephropathy by Inhibiting mTORC1 in a Mouse Model of Type 1 Diabetes

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Introduction: Diabetic-nephropathy (DN) is a leading cause of ESRD. In T2D, treatment with sodium-glucose-cotransporter-2-inhibitors (SGLT2i) prevents DN-progression; however, their effects on DN in T1D are unknown. We hypothesize that in diabetes, increased glucose-uptake to renal proximal-tubule-cells (RPTCs) stimulates mTORC1, a nutrient-sensor regulating cellular-stress, resulting in tubule-interstitial injury. SGLT2i may protect against DN through inhibition of mTORC1 in RPTCs.

Aim: Studying the effects of hyperglycemia and SGLT2i (dapagliflozin) on mTORC1 in RPTCs and its impact on DN in T1D *Akita*-mice.

Methods: We lineage-traced RPTCs by generating wild-type (WT) and *Akita*-mice expressing YFP in RPTCs. Dapagliflozin (5 mg/kg/day) was administered to 2-month old *Akita* for 72h or 12weeks, followed by Western-blotting and immunostaining for phospho-S6 (mTORC1-activity) and markers of tubular-injury, inflammation and fibrosis. Kidney-function was assessed by serum-creatinine, BUN and albuminuria.

Results: *Akita*-mice developed DN evident by increased creatinine, BUN, albuminuria and glomerular-hypertrophy. In 2-month old mice, phospho-S6 was present mainly in RPTCs both in WT and *Akita*-mice. Phospho-S6 staining of lineage-traced RPTCs was increased in diabetic-mice compared to controls. Incubation of RPTC-line LLC-PK1 at high-glucose increased mTORC1-activity, whereas dapagliflozin prevented this. In diabetic-animals, expression of tubular-injury and inflammation markers was increased. Three-month treatment with dapagliflozin decreased RPTCs-mTORC1 activity, tubular-injury, inflammation, fibrosis and tubular-atrophy and improved kidney-function.

Conclusion: In T1D, tubular-injury and inflammation appears early. mTORC1-activity is high in RPTCs, further increasing by hyperglycemia. SGLT2i inhibits mTORC1 in RPTCs, along with decreased tubular-injury, inflammation and fibrosis, with subsequent amelioration of nephropathy. SGLT2i-treatment can become a powerful mean to prevent DN in T1D.

Diabetic Ketoacidosis (DKA) induced by Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2-i) : The Israeli experience

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BACKGROUND

Sodium Glucose Co-Transporter-2 inhibitors (SGLT2-i) are medications for the treatment of Diabetes Mellitus (DM). Their effectiveness in reducing hyperglycemia and improving cardiovascular outcomes is well established. However, there is increase in Diabetic Ketoacidosis (DKA) risk during the use of these medications. DKA is a life threatening event, requires immediate intensive medical treatment. Until now, there is no observational data about SGLT2-i induced DKA in Israeli population.

AIM

To study the cases of SGLT2-i induced DKA those were reported in Israel until December 2018 and characterize risk factors for this event.

METHODS

A retrospective analysis of all cases that were reported to Israel Ministry of Health (MOH) between 2015-2018. The cases were reported by medical teams and pharmaceutical companies.

RESULTS

During the described period, MOH got 92 case reports of DKA in patients receiving SGLT2-i. Mean age 60±12, 55% females. 30(32%) were reported by medical teams and the rest by pharmaceutical companies. DM type was reported in 53 cases, 12(23%) were type I and 41(77%) type II. Risk factors for DKA were reported in 45 cases: Acute infection 16(36%), vomiting/diarrhea 14(31%), surgery/procedure 6(13%). 2 cases of death were reported, even though there is insufficient data to determine whether the death is related to the medication.

CONCLUSION

DKA is an important and dangerous adverse event of SGLT2-i medications, reported in 92 patients in Israel. It seems there are prominent risk factors for this event. Physicians should evaluate the risk for DKA before choosing medical treatment for specific diabetic patient.

The Relationship Between Maternal Glucose Variability During Pregnancy & Neonatal Birthweight Percentile in Pre-Gestational Diabetic Women

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Introduction

Pre-gestational diabetes mellitus (PGDM) is a major risk factor for fetal overgrowth. Interestingly, even in relatively well controlled PGDM women, as determined by average glucose indices such HbA1c, there is an increased rate of LGA. Glucose variability (GV) has emerged as an important independent risk factor for several diabetes complications. The aim of this study was to determine the relationship between maternal GV and neonatal birth percentile.

Methods

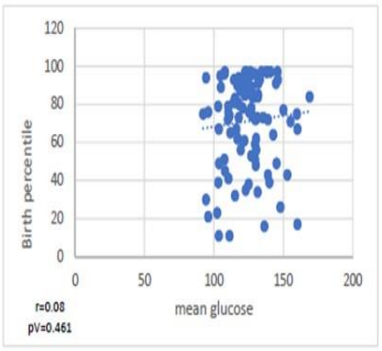
This was a historical prospective study. The study included all consecutive pregnant women with pre-gestational T1DM and T2DM monitored in a single tertiary care center. Clinical and demographic variables as well as data regarding glucose control were prospectively recorded. Mean, standard deviation (SD) and coefficient of variance (CV) of glucose values were calculated for the whole pregnancy of each woman in each pregnancy. Pearson correlations between glucose control indices and birth percentile were analyzed.

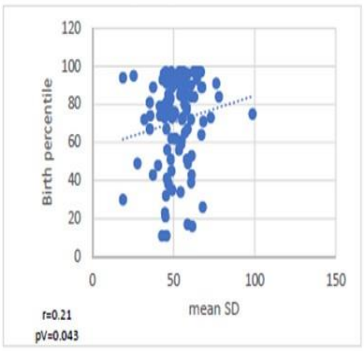
Results

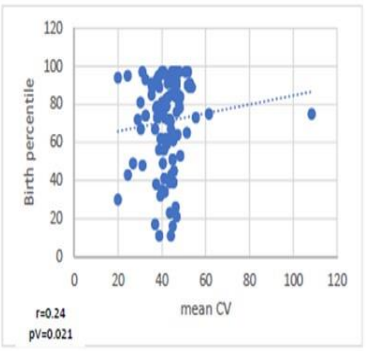
There was a statistically significant positive correlation between birthweight percentile and SD (r=0.28, pV=0.0017) and CV (r=0.21, pV=0.019) of glucose values throughout pregnancy. No correlation between birthweight percentile and mean glucose values was obtained. The association between the SD of glucose values and birthweight percentile remained statistically significant after adjustment for maternal age, pre-pregnancy BMI, duration of diabetes and preeclampsia. Similar findings were noted when the analysis included only patients with CGM.

Conclusion

There is an association between maternal glucose variability (SD and CV) during pregnancy and neonatal birth percentile**.** Intervention studies are warranted in order to elucidate if reduction of GV may prevent LGA and macrosomia in pregnant women with PGDM.


Birth percentile
mean glucose
r=0.08
pV=0.461


Birth percentile
mean SD
r=0.21
pV=0.043


Birth percentile
mean CV
r=0.24
pV=0.021

Endoscopic Ultrasound Guided Radiofrequency Ablation (EUS-RFA) as a Novel Therapeutic Approach in Highly-Selected Pancreatic Neuroendocrine Neoplasms (pNENs) Patients: Preliminary Report.

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Introduction: EUS-RFA is rapidly emerging as a possible treatment alternative for patients with pNENs who are poor surgical candidates. Aim(s): To summarize our experience in terms of feasibility, safety and efficacy of EUS-RFA in a cohort of patients with functional and non-functional pNENs. Materials and methods: Retrospective case series of pNENs patients treated with EUS-RFA at two tertiary referral centers in Israel between March 2017 and October 2018. Results: Eighteen consecutive pNENs patients that underwent EUS-RFA have been included (11 males, median age of 62.5 (range 28 - 82)). A total of 27 lesions with a median size of 13 mm (range 4.5-29) were treated. The location of the target lesion was: head (n=10), body (n=8), uncinate process (n=5) and tail (n=2); in two patients, synchronous liver and lymph node metastasis underwent RFA. Functionally, the tumors were nonfunctional pNENs and insulinomas in 11 and 7 patients respectively. All tumors were well-differentiated based on Ki-67. Technical success, defined as post RFA changes in tumor vascularity and/or tumor necrosis on surveillance imaging was reported in 26/27 lesions. Normalization of glucose levels was observed in all (7/7) insulinomas within 24h. There were no major complications 48h post-RFA. Two patients developed mild pancreatitis post-RFA that resolved within 72 hours. No recurrences were observed during a median follow up of 6 months (range 1–20m). Conclusion: EUS-RFA for highly selected pNENs patients who cannot or do not want to undergo surgical resection appears to be safe and feasible. Prospective studies comparing RFA with surgical excision, including larger cohorts of patients and longer follow-up periods, are warranted to establish the role of EUS-RFA in the treatment algorithm for pNENs.

Molecular and Functional Investigation of the Differential Regulation of LH and FSH Cells in Fish

Lian Hollander-Cohen[1], Matan Golan[2], Patrice Mollard[2], **Berta Levavi-Sivan**[1]
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Pituitary gonadotropes play a crucial role in the hypothalamic-pituitary-gonad axis in fish by secreting follicle-stimulating hormone (FSH) or luteinizing hormone (LH), which regulate gametogenesis and ovulation. LH and FSH are secreted from the same gonadotrope population in mammals. However, in fish, LH and FSH producing cells form distinct populations, allowing us to dissect and investigate the differential mechanisms controlling the release of each hormone. Using transgenic Nile tilapia (*Oreochromis niloticus*) with fluorophores expressed in LH and FSH cells we were able to characterise the organisation of those cells in the pituitary, and to separate each gonadotrope population using fluorescence-activated cell sorting (FACS) technology. We analysed and compared the expression profiles of these isolated LH and FSH cells to negative cell population containing all pituitary cells which are not gonadotropes by performing RNA sequencing. Relative to the negative cell population, 514 genes were exclusively expressed in LH cells, 1448 were exclusively expressed in FSH cells, and 140 genes were common to both. Of these exclusive genes in LH and FSH cells, 43 and 28, respectively, were G-protein coupled receptors, implicating differential hormonal control of each cell population. Using transgenic zebrafish (*Danio rerio*) expressing genetically encoded calcium indicator, we monitored LH cells and FSH cells activity *ex vivo* and found very distinctive basal and GnRH-induced calcium activity for each cell population. Our data provides molecular and functional evidence for the differential mechanisms controlling gonadotropin secretion in fish.

Tissue Turnover Dynamics in the HPA Axis Explains the Timescale of Weeks in Clinically Relevant Conditions

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[2]*Computer Science, Weizmann Institute of Science, Israel*

Background: Clinically relevant phenomena involving the HPA axis often have timescales of weeks, including steroid addiction, postpartum hormone imbalance and mood disorders. The origin of this weeks-long timescale is unclear, given that the hormones have short (hours) lifetime.

Aim: To provide a mechanistic explanation for HPA-axis clinical effects that last for weeks.

Methods: We use mathematical modelling and test it using large-scale electronic medical records, MRI measurements of gland size and data from the literature.

Results: We present a model of the HPA dynamics, which shows that the gland change their mass on the timescale of weeks due to a negative feedback loop in which the corticotrophs and adrenal cortex cell mass regulate each other by means of the trophic effects of CRH and ACTH. This predicts seasonal oscillations in cortisol that peak in the spring, in agreement with large-scale blood test data. The model also correctly predicts the overshoot in ACTH after a few months of steroid withdrawal, and the postpartum imbalance in ACTH and cortisol.

Conclusions: This work suggests that clinical conditions such as glucocorticoid addiction and mood disorders such as postpartum depression and seasonal affective disorder might have a partial mechanistic explanation related to atrophy and hypertrophy of the adrenal and pituitary glands. More generally, endocrine glands may form networks in which gland sizes co-regulate each other, showing changes over weeks that can affect physiology.

Anatomic Site of Pancreatic Neuroendocrine Tumors as a Prognostic Marker

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

Introduction

Patients with pancreatic neuroendocrine tumors (PNET) have variable prognosis, even with comparable tumor grade and stage.

Aim

We aimed to evaluate the prognostic significance of primary tumor location within the pancreas in patients with PNET.

Methods

A retrospective analysis of patients with PNET documented in the Surveillance Epidemiology and End-Results (SEER) database between 2004-2015, including patients with determined stage, grade and tumor anatomical site. We analyzed survival according to disease-specific mortality and performed multivariable cox regression analysis, adjusting for variables that were significantly different in univariate analysis.

Results

The current analysis included 4,171 patients (1,839 women [44.1%], median age strata 60-64 years). Comparison between PNETs located at the head vs. body/tail of the pancreas showed comparable tumor diameter and similar distributions of ethnicity, gender and age, but higher rates of grade III and IV PNETs (by SEER definitions) in pancreatic-head NETs (13.2% vs. 6.6%, and 4.4% vs. 1.9%, respectively, p 0.001). Head of pancreas NETs were more likely to be locally advanced (32.2% vs 19.9%) with no difference in distant metastases (36.4% vs. 33.5%, respectively, p 0.001). Patients with PNETs of the head had higher risk for disease-specific mortality compared with patients with body/tail of the pancreas, both in univariate (log-rank test, p 0.001) and multivariable analysis (Hazard ratio 1.53, 95% confidence interval 1.26-1.88, p0.001). Disease stage, year of diagnosis and grade were also statistically prognostic in the multivariable analysis.

Conclusion

Pancreatic anatomical site should be considered as a prognostic factor for in patients harboring PNETs.

Ovarian adrenal rest tumors in congenital adrenal hyperplasia:

Is medical treatment the first line option?

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[6]*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, Israel*

Introduction: Ovarian adrenal rest tumors (OARTs), in contrast with testicular adrenal rest tumors, are very rare. Up to date, 13 cases were reported in the literature; all treated surgically.

Aim: We describe a case of a young female with uncontrolled classical congenital adrenal hyperplasia (CCAH), presenting with bilateral OARTs, successfully treated with steroid replacement.

Methods: Data on clinical history and biochemical work-up was obtained from medical records.

Case presentation: A 20 years old women presented with severe abdominal pain, vomiting, diarrhea, and fever. She was known to have 21OH-CCAH. As a result of poor compliance, 6 months before her admission hirsutism worsened and amenorrhea, hyperpigmentation, and weakness developed. ACTH levels were 278

Conclusion: OARTs are rare tumors with a poorly known natural history, and surgery has been the first option in the few reported cases. We demonstrate here that medical treatment is a good alternative, leading to significant tumor shrinkage over a short period.

Hyperandrogenism in a 13-year-old Girl due to Glucocorticoid Receptor Mutation

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[3]*Rappaport Faculty of Medicine, Technion, Israel*

Glucocorticoid resistance syndrome (GRS) is a rare genetic disorder caused by inactivating mutations of the *NR3C1* gene encoding the glucocorticoid receptor. The phenotypic spectrum is broad but typically includes symptoms of adrenal insufficiency, mineralocorticoid excess and hyperandrogenism. So far, about 20 different mutations in *NR3C1* presenting with the GRS phenotype have been reported.

We report a 13-year-old girl that presented with severe hirsutism and clitoromegaly. No suppression of cortisol following short overnight dexamethasone test, repeated elevated urinary free cortisol (UFC) and elevated ACTH indicated a diagnosis of Cushing syndrome. Imaging evaluation by brain and abdominal MRI revealed normal pituitary and adrenal glands. Based on the contradiction between the phenotype, with absence of manifestations of Cushing syndrome, and the laboratory findings that indicated Cushing syndrome, GRS was suspected.

Sanger sequencing of *NR3C1* identified a previously reported heterozygous mutation, c.1759_1762dupTTAC; p.His588Leufs*5, which results in a frameshift and stop codon 5 amino acids forward, in the proband and in her father. Other family members were negative for the identified mutation. The father was asymptomatic but had elevated 24-h UFC. Treatment with a low dose of dexamethasone improved the hirsutism and her well-being.

The reported case demonstrates the unique phenotype of GRS andhighlighted raises awareness of this rare condition. Glucocorticoid receptor sequencing is recommended in cases with discrepancies between laboratory findings that suggest Cushing syndrome and clinical manifestations of hyperandrogenism and mineralocorticoid excess with no symptoms of glucocorticoid excess.

Posterior Pituitary Spindle-cell Oncocytoma: Case Presentation and Literature Review

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[2]*Sackler School of Medicine, Tel Aviv University*

Introduction: Spindle cell oncocytoma (SCO), pituicytoma, granular cell tumor, and sellar ependymoma are rare TTF-1 positive posterior pituitary tumors classified as WHO Grade I, indicating low proliferative potential and high rates of surgical cure.

Aims: To report a case of SCO and review the pertinent literature.

Methods: English and non-English literature was searched, clinical, data were retrieved and summarized.

Results: A 39 years old male presented with complaints of headaches. MRI identified a suprasellar tumor that was initially followed conservatively. Vision and pituitary function were preserved. Symptom exacerbation and evidence of tumor growth led to transsphenoidal surgery. Tumor resection was compromised by profuse bleeding. He developed post-surgical pan-hypopituitarism.

42 publications describing 54 cases of SCO were identified (median age 60 y, 57% males). Presenting symptoms were mostly secondary to mass effect. 67% of tumors were sellar with suprasellar extension, 23% and 9.6% were exclusively intra or suprasellar respectively. All patients underwent surgery, 83% of which was trans-sphenoidal. Mean Ki-67 was 3.4%. Gross total resection was achieved in only 47.8% of cases, with recurrence-free survival time of 116 months [95% CI, 65-167]. After partial resection, event-free survival time was 23 months [95% CI, 12-34]. Nine patients received radiation therapy with mixed results.

Conclusions: Surgical resection of these rare tumors is challenging; surgical cure is infrequent and recurrence rates are high. Based on this literature review, we suggest that WHO classification of these tumors as grade 1 is not accurate, and that a revision should be considered.

Recent advances in deciphering the genetic basis of endocrine hypertension

Felix Beuschlein
UniversitätsSpital Zürich

Most forms of endocrine hypertension are caused by dysregulation of adrenal hormone secretion as evident in primary aldosteronism, hypercortisolism or pheochromocytoma related catecholamine excess. The advent of new genetic techniques that allow for high-throughput sequencing in surgical tumor tissues and germline DNA has boosted progress in many fields of biomedical research. The technique has been proven to be particularly fruitful in the area of endocrine tumors with many new driver genes being identified over the last years that are involved in cell growth but more importantly in hormonal autonomy. For the adrenal gland examples account for aldosterone and cortisol producing adrenal adenomas, adrenocortical carcinomas as well as pheochromocytomas. In succession with these insights in genetic contributors in adrenal pathophysiology, deep clinical and biochemical phenotyping has allowed for genotype/phenotype correlations that provide further mechanistic concepts. As to be expected, adjustment of clinical management in patients with adrenal form of hypertension that would rely solely or in great part on genetic information is lacking behind. The presentation will provide an update on the current state of the art in personalized approaches and the yet to be achieved spectrum of precision medicine for patients with endocrine hypertension.

Symposia 4

New Directions in Growth Hormone-IGF1 Research (Monday, April 8, 2019 10:40)

The Role of the IGF1 Pathway in Neurodegenerative Disorders: Therapeutic Opportunities

Ehud Cohen

Aging manipulation is an emerging strategy aimed to postpone the manifestation of late-onset neurodegenerative disorders such as Alzheimer's (AD) and Huntington's diseases (HD), and slow their progression once emerged. Reducing the activity of the IGF-1 signaling cascade, a prominent aging regulating pathway, protects worms from proteotoxicity of various aggregative proteins, including the AD-associated peptide, Aβ and the HD-linked peptide, polyQ40. Similarly, IGF1 signaling reduction protects mice from AD-like disease. These discoveries suggest that IGF1 signaling inhibitors can serve as new drugs for the treatment of neurodegenerative maladies. We discovered that NT219, a novel IIS inhibitor, mediates a long-lasting, highly efficient inhibition of the IGF1 signaling cascade by a dual mechanism; it reduces the auto-phosphorylation of the IGF1 receptor and directs the Insulin receptor substrates 1 and 2 (IRS 1/2) for degradation. NT219 treatment promotes stress resistance and protects nematodes from AD- and HD-associated proteotoxicity without affecting lifespan. Our discoveries strengthen the theme that the inhibition of IGF1 signaling has a therapeutic potential as a cure for neurodegenerative maladies and point at NT219 as a promising compound for the treatment of these disorders through a selective manipulation of aging.

Symposia 5

Mechanisms of Metabolic Surgery and Incretin Therapies for Diabetes and Obesity

(Monday, April 8, 2019 14:10)

GIP Regulation of Body Weight and Inflammation

Sigal Fishman
Sourasky Medical Center, Tel Aviv

Enteroendocrine cells relay energy-derived signals to immune cells to signal states of nutrient abundance and control immunometabolism. Emerging data suggest that the gut-derived nutrient-induced incretin glucose-dependent insulinotropic polypeptide (GIP) operates at the interface of metabolism and inflammation. Nevertheless, multiple studies in difference models have yielded controversy concerning the role of GIP in the control of body weight and inflammation. Part of them have attributed anti-obesogenic and anti-inflammatory properties to GIP and other have shown the opposite effects. In our recent study we show that high fat diet (HFD)-fed mice with immune cell-targeted GIP receptor (GIPR)-deficiency exhibit greater weight gain, insulin resistance, hepatic steatosis, and significant myelopoiesis concomitantly with impaired energy expenditure and inguinal white adipose tissue (WAT) beiging. S100A8 protein expression was increased in the WAT of mice with immune cell-targeted GIPR-deficiency. Of note, direct administration of S100A8/A9 (calprotectin), significantly has reduced beiging in inguinal fat of mice challenged with cold conditions. Importantly, co-deletion of GIPR and S100A8/A9 in immune cells ameliorated the aggravated metabolic and inflammatory phenotype following HFD. Specific GIPR deletion in myeloid cells identified this lineage as the target of GIP effects. Conversely, GIP directly down-regulated S100A8 expression in adipose tissue macrophages. Collectively, our results identify a myeloid-GIPR-S100A8/A9 signaling axis coupling nutrient signals to the control of inflammation and adaptive thermogenesis. The results of the presence study may bear therapeutics implication enlightening GIPR as a target to pharmaceutical intervention.

Symposia 6

Central Control of Reproductive Function (Monday, April 8, 2019 14:10)

Metabolic-Reproductive Connections: Molecular Basis for Disordered Puberty in Malnutrition and Obesity

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Puberty is a sophisticated developmental event, controlled by precise regulatory networks that integrate peripheral and internal signals to drive the timed activation of the brain centers driving the reproductive axis. Although the timing of puberty in humans and other mammals is genetically determined, it is highly sensitive also to numerous internal and external cues, among which metabolic and nutritional signals are especially prominent. Compelling epidemiological evidence suggests that alterations of the age of puberty are becoming more frequent in humans, via as yet unknown mechanisms. However, the escalating prevalence of obesity and other metabolic/feeding disorders has been blamed as major contributing factor. Over the last decade, a large body of evidence has documented the fundamental role of hypothalamic neurons producing kisspeptins (encoded by the Kiss1 gene) as master elements in the neuroendocrine pathways controlling puberty. Kiss1 neurons seemingly operate also as conduits for at least part of the metabolic regulation of puberty. In this presentation, we will review recent findings unveiling the important role of key cellular metabolic sensors, such as AMP-activated protein kinase (AMPK), the master cellular sensor activated in conditions of energy insufficiency, and the fuel-sensing deacetylase, Sirt1, as major components for the metabolic modulation of female puberty onset. Our data point out that these are major molecular hubs acting in Kiss1 neurons, whose deregulation may explain the perturbations of puberty commonly observed in conditions of metabolic stress, ranging from subnutrition to obesity.

Symposia 6

Central Control of Reproductive Function (Monday, April 8, 2019 14:10)

Gonadotropins Role in Mediating the Medical Complications of Anorexia Nervosa

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Anorexia nervosa (AN) is a severe chronic psychiatric disorder with an onset usually during adolescence, with current lifetime prevalence of 2.2%. AN is characterized by self-imposed malnutrition, weight loss, and an intense fear of gaining weight, despite being underweight. The disease may serve as a valuable model for studying the effect of caloric restriction during adolescence, since in AN patients undernutrition occurs in the absence of other physical illness, and weight rehabilitation is planned and controlled.

AN is associated with multiple medical complications involving many organ systems including the cardiovascular, gastrointestinal, renal, pulmonary, hematologic, dental and neurologic. Furthermore, the mortality rate of young subjects with AN is 12 times higher compared to their peers. Endocrine abnormalities include growth hormone resistance with low IGF-1 levels, hypothyroxinemia, relative hypercortisolemia, changes in appetite regulating hormones, including leptin, ghrelin, and peptide YY, and hypogonadotrophic hypogonadism. Low gonadotropins levels and the ensuing hypoestrogenemia contribute to abnormalities in linear growth, and have a major effect on bone metabolism, leading to low bone mass, impaired bone microarchitecture, and increased risk for fracture. Hypogonadism may also negatively impact cognition, emotions, sleep quality, and mood. Lower parity relative to the general population and siblings, a higher rate of unplanned pregnancy, and increased risk for obstetric and perinatal complications have been observed, although the mechanism has not been elucidated. The best strategy to improve all biologic outcomes is weight and menstrual recovery. Failing that, physiological estrogen replacement may improve bone accrual rates and measures of trait anxiety in adolescents with AN.

Poster Presentation (Sunday, April 7, 2019 10:20)

Central Precocious Puberty as Presenting Sign of Non-Classical Congenital Adrenal Hyperplasia - Prevalence and Clinical Characteristics

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Context: Central precocious puberty (CPP) may be the first presentation of non-classical congenital adrenal hyperplasia (NCCAH) in girls. Data on the prevalence and the clinical phenotype of CPP associated with NCCAH are sparse.

Objectives: To study the clinical and laboratory characteristics that could differentiate between idiopathic CPP and CPP associated with NCCAH, and to determine the prevalence of NCCAH among girls with CPP.

Design: Case-control study.

Setting: A tertiary pediatric endocrinology institute.

Participants and Methods: From 2008 to 2017, 147 girls who had undergone stimulation tests with luteinizing-hormone-releasing-hormone and Synacthen were diagnosed as CPP, with seven (4.8%) eventually diagnosed as NCCAH. The latter 7 together with 30 girls presenting as CPP between 1984-2008 and eventually diagnosed as NCCAH comprised the NCCAH group. Demographic, anthropometric, clinical and laboratory data of the girls in the NCCAH group were compared to those of the 140 with idiopathic CPP (ICPP group).

Results: No between-groups difference was found in height, weight, BMI, bone age and Tanner stage. Mean basal androstenedione, DHEAS and 17-OHP were significantly higher in girls with NCCAH, with an overlap between groups, while stimulated cortisol was higher in the ICPP group. Of girls presenting with true CPP throughout a decade, NCCAH was diagnosed in 4.8%.

Conclusions: NCCAH was found in 4.8% of girls with true CPP, and no one parameter could differentiate between the diagnoses. Thus, in girls with true CPP, in populations where NCCAH is prevalent, assessment of adrenal androgens is required and an ACTH test should be considered.

Poster Presentation (Sunday, April 7, 2019 10:20)

A Seminoma with Entrapped Nerve Ganglion Masquerading as a Paraganglioma

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Background: The differential diagnosis of retroperitoneal tumors includes lymphoid, germ cell and neurogenic tumors including paraganglioma. Paragangliomas are rare neuroendocrine tumors of the autonomic nervous system, which usually secrete catecholamines and their metabolites. Clinical features include hypertension which may be paroxysmal, headaches, sweating and palpitations. Treatment is by curative surgical resection.

Case study: A fifty-seven year old man with a history of controlled hypertension presented with paroxysms of tachycardia, flushing, high blood pressure and headache. Ambulatory blood pressure monitoring showed uncontrolled fluctuant hypertension with normal `asleep dip`. Abdominal CT demonstrated a 6.1cm mass in the right retroperitoneum with adjacent lymphadenopathy. Paraganglioma was suspected. Urinary 24-hour collection demonstrated mildly elevated normetanephrine (575mcg/24hrs, norm 5-290) and VMA (8.3mg/24hrs, norm 0.5-6.6). 68-Gallium DOTATATE PET/CT showed weak uptake in the retroperitoneal mass and no other mass lesions. Surgical excision was performed with diagnostic and curative intent, following preparation with alpha-adrenergic blockers. Post-operatively, hypertension and paroxysmal symptoms disappeared. The histopathology report described seminoma with an entrapped large ganglion within the tumor.

Conclusion: We describe a retroperitoneal seminoma with an entrapped ganglion causing hypertension and paroxysmal symptoms, with laboratory and imaging features compatible with paraganglioma. There were, nevertheless, inconsistencies including mild elevation of normetanephrine levels, and imaging features including lack of vascularity and weak DOTATATE uptake. In conclusion, when encountering a retroperitoneal mass with hypertension and paroxysmal features but inconclusive biochemical test results and imaging features, the rare possibility of mechanical pressure on a ganglion should be considered.

Poster Presentation (Sunday, April 7, 2019 10:20)

Pheochromocytoma: Positive Predictive Values of Mildly-elevated Urinary Fractionated Metanephrines and Current Features at Diagnosis.

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Objective: The specificity of elevated urinary fractionated metanephrines (UFM) in patients screened for pheochromocytoma/paraganglioma (PPGL) is suboptimal. This study sought to investigate the diagnostic utility of different thresholds of elevated UFM and to analyze current features of PPGL in a large cohort of community-dwelling patients.
Methods: Retrospective file review of all patients who performed UFM tests in 2012-2017 at Maccabi Health Services, and their urinary levels of metanephrines and/or normetanephrines were ≥1.5x the upper normal limit (UNL).
Results: Of the 10164 subjects referred to UFM testing, levels of 1.5xUNL and ≥2xUNL were found in 286 (2.8%) and 143 (1.4%), respectively. Sixty patients were subsequently diagnosed with PPGL (mean age 51.8±14.3, 65% females). Of these, 59 (98.3%) had UFM ≥2xUNL, yielding a positive predictive value (PPV) of 41.3% (59/143) for this threshold. Only one patient with paraganglioma had UFM level of 1.5-2xUNL. The main reason for screening, in 51.7% (31/60) of PPGL patients, was adrenal incidentaloma. Mean metanephrines/normetanephrines levels were 6.6±9xUNL and 6.1±8.9xUNL, respectively (median: 2.9xUNL and 2.5xUNL, respectively). Extra-adrenal tumor was detected in 6 patients (10%); bilateral masses and malignant PPGL in one patient, each. The classical triad of pheochromocytoma (headaches, sweating, tachycardia) was present in only one patient and 34 (56.7%) had none of these symptoms.
Conclusions: Most PPGL patients are currently diagnosed due to the detection of an adrenal incidentaloma. While in patients with UFM ≥x2UNL the PPV for PGGL justifies a thorough diagnostic assessment, in patients with milder elevations the probability of PPGL diagnosis is very low.

Poster Presentation (Sunday, April 7, 2019 10:20)

Higher C-peptide Levels and Glucose Requirements may Identify Neonates with Transient Hyperinsulinism Hypoglycemia Who Will Benefit from Diazoxide Treatment

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Background: Neonates with transient hyperinsulinism usually do not require treatment due to its self-limited clinical course, but some may benefit from diazoxide treatment which inhibits insulin secretion.

Objectives: To find factors that may serve as a clinical tool to identify neonates with transient neonatal hyperinsulinemia who may benefit from diazoxide treatment.

Patients & methods: Retrospective chart review of neonates with transient hyperinsulinism hypoglycemia who were born between 01/01/2015-30/04/2018.

Results: The study included 141 neonates (93 males). Thirty-four (24%) were treated with diazoxide. Mean gestational age (GA) was 36.0±2.7 weeks and mean birth weight (BW) was 2.175±0.699 Kg. The diazoxide-treated and untreated groups were similar in perinatal (GA, BW, Apgar score) and maternal factors (age, number of pregnancies, number of deliveries, diabetes, hypertension, eclampsia). Diazoxide treatment was started at mean age of 14.6±8.0 days and discontinued on day 49.2±40.2 of life. The maximal diazoxide dose was 7.1±2.3 mg/kg/day. Diazoxide-treated neonates required a higher glucose infusion rate (GIR) compared to untreated neonates (16.6±3.4 vs 10.4±4.0 mg/kg/min, p0.01), had a longer duration of intravenous fluids (15.9±19.3 vs 7.8±6.5 days, p0.01), longer duration of hospitalization (32.8±22.7 vs 20.4±13.4 days, p0.01), longer duration of carbohydrate supplementation (38.9±40.4 vs 17.8±21.4 days, p0.01), and higher mean C-peptide levels (1.4±0.9 vs 0.8±0.5 ng/ml, p0.01). Their insulin levels tended to be higher (3.5±2.9 vs 2.2±3.8 µU/ml, p=0.07). **Summary:** Higher C-peptide levels and higher GIR requirement may serve as a clinical tool to identify neonates with transient hyperinsulinism hypoglycemia who may benefit from diazoxide treatment.

Poster Presentation (Sunday, April 7, 2019 10:20)

A Short Pheochromocytomas (PCC) and Paragangliomas (PGL) PPGLs Series from a 2018 Perspective

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***Introduction*:** WHO reclassified PPGLs in 2017 to emphasize their malignant potential. ***Aims*:** Report PPGLs cases diagnosed and treated at our institute. ***Case Reports*: (1)** 74-yo female w/tachycardia, hyperglycemia, HTN, MI, BreastCa, TCC. Metanephrines x4UNL, 2.8-cm Rt-adrenal mass, Dopa-PET+, cured after laparoscopic adrenalectomy (LA). Patho: PCC focally-invasive, Ki67 2.6%. Time-to-Sx 4 mo, postOp FU 28 mo, no recurrence. Genetic consultation (GC) not done **(2)** 49-yo female, asymptomatic, 8-cm Rt-adrenal incidentaloma, metanephrines x30UNL. Patho: PCC focally-invasive. Cured after LA. Time-to-Sx 32 mo, postOp FU 6 mo, no persistence. GC pending. **(3)** 73-yo female w/PHPT, HTN, 4-cm Rt-PGL, dopamine x2UNL, MIBG+. Cured after OA. Time-to-Sx 6 mo, postOp FU 108 mo, no recurrence, no GC. **(4)** A 79-yo female w/HTN, hyperglycemia, psychiatric disorder. Normetanephrines x11UNL, 4-cm non-invasive Rt-PCC, Ki67 1-2%, cured after LA. Time-to-Sx 6 mo, postOp ICU 2 days, postOp FU 1 mo, no persistence, no GC. **(5)** 65-yo female w/palpitations, hyperglycemia, CVA, HTN, 2.5-cm non-invasive Rt-PCC, normetanephrines x1.5UNL, Dopa-PET+. Cured after LA. Time-to-Sx 6 mo, postOp FU 6 mo, no persistence, no GC. **(6)** 74-yo male w/HTN, CVA, AFib, incidental 3.5-cm Rt-retroperitoneal mass, metanephrines x6UNL, suspected PGL on MIBG. 4-yrs on medical treatment, stable, no growth, refused Sx, no GC. **(7)** 62-yo male w/HTN and 7-cm suspicious Rt-retroperitoneal mass. No preOp workup, R1 after LA. Patho: PGL, Ki67 3-5%. PostOp: Dotate-PET+, x3UNL methoxytyramine, persistent, GC pending. ***Conclusion*:** Since PPGL`s are now considered to be potentially malignant tumors, higher awareness, longer FU and a more detailed pathological report are needed.

Poster Presentation (Sunday, April 7, 2019 10:20)

ProGRP is an Effective Marker for Disease Monitoring in Lung Carcinoids with Non-Informative Chromogranin A: Lessons from Clinical Practice

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Introduction: The histologic classification of lung carcinoids (LCs) highlights its role as major prognostic factor. However, in the absence of sensitive biomarkers to effectively predict tumor behavior, long-term imaging surveillance is recommended for disease monitoring. Limited data suggest that progastrin-releasing peptide (ProGRP) may have diagnostic & monitoring utility in LCs. **Aim:** To evaluate the possible role of ProGRP, as a biomarker for LCs surveillance. **Materials and methods:** Retrospective analysis of consecutive LCs patients treated in an ENETS Center of Excellence with regard to clinico-pathological parameters, treatment outcomes and their correlation with ProGRP and CgA. **Results:** 35 patients (pts) were studied (23 women; median age of 62y with a median follow up of 47m). TCs and ACs were diagnosed in 43% and 57% of pts, respectively. The disease was localized in 31% & metastatic in 69% of cases. 71% of pts were already pretreated at the time of the first ProGRP evaluation. Disease status at first ProGRP measurement was: no evidence of disease (NED, 20%), stable disease (SD, 23%), progressive disease (PD, 57%). The NED group had normal ProGRP & CgA. In the SD group, ProGRP was increased in 62% vs 38% increase in CgA, while in the PD group 70% had increased ProGRP vs 35% with elevated CgA. Overall, ProGRP was increased in 50% of pts with evidence of disease, all with normal CgA. **Conclusion:** ProGRP seems to be a valuable biomarker for monitoring patients with LCs, mainly when CgA is non-informative.

Poster Presentation (Sunday, April 7, 2019 10:20)

Lower All-cause Mortality Rates in Patients Harboring Pituitary Carcinoma (PitCa) Following the Introduction of Temozolomide

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Introduction

Pituitary carcinomas (PitCa), defined by pituitary neoplasm with distant metastases, are rare, and the reported survival after diagnosis is poor, with a 1-year survival of 66%. Temozolomide, an oral alkylating agent, was approved for the treatment of aggressive pituitary tumors in 1999, but so far its safety and efficacy has only been evaluated based on case reports and one systemic review.

Aim

To evaluate how Temozolomide introduction has affected survival of patients with PitCa.

Methods

Retrospective analysis of the Surveillance Epidemiology and End-Results database, including patients diagnosed histologically with PitCa, and radiologically with pituitary adenomas (PitAd) between 1973-2015. Age-adjusted survival analyses were performed, comparing all-cause mortality (ACM) rates before 2000 ("period 1"), and during 2000 or later ("period 2", following Temozolomide introduction), and between patients harboring PitCa vs. PitAd.

Results

Among 107 patients, eighteen (16.8%) harbored PitCa. Sixteen were diagnosed during period 1 (13/3 PitAd/PitCa) and 91 - during period 2 (76/15). PitCa diagnosis rates were comparable between the periods, while regional extension was more frequent during period 2 (18.8% vs. 61.5%, respectively, p=0.002).

Patients harboring PitCa had higher ACM risk in period 1 vs. 2 (log-rank test, p=0.004), while ACM rates for the entire cohort were comparable between the two periods (p=0.25). Moreover, ACM rates were higher among patients harboring PitCa vs. PitAd during period 1 (p=0.001), but not in period 2 (p=0.54).

Conclusion

In this large cancer-database analysis we show improved overall survival in patients harboring PitCa in the years following the introduction of temozolomide.

Poster Presentation (Sunday, April 7, 2019 10:20)

Three Years Persistence with Denosumab as Osteoporosis Therapy in Maccabi Healthcare Services

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Background

Previous studies on short term persistence with Denosumab as osteoporosis therapy showed higher persistence compared to oral bisphosphonates.

Aim

To assess the long term persistence rates with Denosumab in a large, un-selected population.

Methods

This retrospective study utilized the computerized database of Maccabi healthcare services. Data were collected for new Denosumab initiators from January 2012 to June 2016 with at least two dispenses, followed until December 31, 2017 for 12-36 months. We excluded patients with malignancies, chronic kidney disease, previous anabolic therapy and chronic glucocorticoid treatment. Discontinuation was defined as a gap of at least 9 months from the previous injection, and persistence ≥70% coverage.

Results

A total of 1,277 eligible Denosumab initiators were identified, 96% of which were women, with a mean age of 70.8 years old (SD=8.8). A total of 86.8% of them received a second Denosumab injection within less than 9 months, almost 2-fold comparing to 48.2% persistence with oral bisphosphonates in the first year. However, in the 2'nd and 3'rd years of follow-up Denosumab persistence rates dropped to 64.4% and 38.4%, respectively, similar to oral bisphosphonates persistence with 32.7% in the third year.

Conclusions

In this real-world, population-based study, patients treated with Denosumab exhibited excellent persistence in the first year, which dramatically deteriorated in the following second and third years. Further research is needed to explore the barriers for long term persistence with Denosumab, and assistive tools may be in order to help physicians and patients in maintaining treatment continuity after the first year of treatment.

Poster Presentation (Sunday, April 7, 2019 10:20)

The Enigma of Unexpected High BMD in an Anorectic Patient

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A 36 year-old female patient with Anorexia Nervosa since age 12 was referred to the metabolic bone disease clinic due to premature severe painful disabling bilateral hip osteoarthritis and diffuse skeletal osteosclerosis. No family history of metabolic bone disease or any other endocrine or non-endocrine condition. DXA scan revealed an extremely high bone mass at the lumbar spine with T SCORE of +4.2 and T SCORE of +0.1 at the femoral neck, with a significant increase in BMD compared to 4 years earlier. Serum level of calcium, phosphor, magnesium, albumin, creatinine and 25-OH vitamin D were normal. Due to severe disability the patient underwent bilateral hip replacement. Pathologic evaluation of the specimen revealed pathologic bone remodeling with thick and irregularly distributed lamellar and woven cortical and trabecular bone with no evidence of metabolic bone disease. The plain abdominal X-ray films demonstrated a radio-opaque material in the large intestine. The presumptive diagnosis of skeletal fluorosis was made. The bone specimen that was removed during surgery was sent to the Israeli Geological Institute and was found to contain an elevated fluoride concentration (3300 mg/Kg compared to 2650 mg/Kg in healthy bones). Confrontation with the patient and her mother confirmed that the patient has been eating at least five to six toothpaste tubes weekly for at least 5 years. A diagnosis of skeletal fluorosis due to excessive toothpaste consumption was made.

Poster Presentation (Sunday, April 7, 2019 10:20)

Bone Loss under Oral Bisphosphonates Treatment in Maccabi Healthcare Services

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Background

The efficacy of oral bisphosphonates in preservation of bone mineral density (BMD) has been demonstrated both in clinical trials as well as observational cohorts, yet this benefit is reduced by low adherence to treatment.

Aim

To characterize and estimate the proportion of patients with bone loss despite high adherence to oral bisphosphonates, in a real-world setting.

Methods

This retrospective study utilized the computerized database of Maccabi healthcare services, and bone mineral density measurements of Assuta hospitals. Data were collected for patients with BMD decrease of at least 5% between two measurements within two years until December 31, 2017. We excluded patients with chronic kidney disease, previous anabolic therapy and chronic glucocorticoid treatment.

Results

We identified 2,579 eligible patients with a BMD decrease of at least 5% within two years, 385 (15%) of them were previously adherent to oral bisphosphonates (≥70% coverage) for at least 6 months. Among those non-responsive, 88.8% were women, with a mean age of 68.8 years old (SD=8.3). According to the T-score in the two BMD measurements, 14.8% of non-responsive shifted from osteopenia to osteoporosis (T-score below -2.5). In addition, 5.5% also had a previous fracture while treated, within two years before the decrease of BMD was measured.

Conclusions

Significant number of patients demonstrated bone loss despite high adherence to oral bisphosphonates. Further studies are required to identify which patients will benefit from alternate treatment to minimize their risk.

Poster Presentation (Sunday, April 7, 2019 10:20)

Hypophosphatemia Following a Ferric Carboxymaltose Injection: an FGF-23 Mediated Process

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Hypophosphatemia following iron infusion has been described in a few case reports and series since 2009. Nevertheless, the clinicians` awareness of this side effect is suboptimal. The precise mechanism is unknown, but probably related to FGF-23 mediated renal phosphate wasting.

Aim: We describe a patient with acute profound hypophosphatemia following a high dose ferric carboxymaltose injection and provide a time course of FGF-23 decline and mineral abnormalities recovery.

Results: A 68-year old man with iron deficiency anemia due to atrophic gastritis, received 1000 mg ferric carboxymaltose injection. Three weeks later, routine blood sample revealed hypophosphatemia (0.9mg/dl), hypocalcemia (7.55 mg/dl), low-normal 25-OH-D (60 nmol/l) and elevated PTH, 67 pg/ml (5-38). Urine phosphate was elevated (583mg/24 hours) with fractional excretion of 52 %. FGF-23 was high, 343 pg/ml (23-95) and 1,25$(OH)_2$VitaminD was inappropriately low, 61 pmol/l (37-158), despite severe hypophosphatemia. The patient was asymptomatic. Treatment with sodium & potassium phosphate, calcium carbonate, cholecalciferol and alpha calcidiol was instituted. FGF-23 gradually declined over 3 weeks. Required supplements doses, adjusted to the serum phosphate, were reduced and the medications were subsequently stopped over 3 months.

Conclusions: This case highlights the importance of timely identification of the possible influence of iron infusion on phosphate homeostasis to avoid unnecessary investigation of other etiologies and to allow proper management. Serum FGF-23 measurement is an important adjunctive to mineral metabolism investigation panel.

Poster Presentation (Sunday, April 7, 2019 10:20)

Longitudinal Follow-up of Bone Density in Children with Inflammatory Bowel Diseases

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Objectives and study: Pediatric inflammatory bowel disease (IBD) patients are prone to low bone mineral density (BMD) and increased risk for fractures. Our aim was to examine the longitudinal changes of BMD during follow up.

Methods: A retrospective longitudinal study of BMD measurements at the lumbar spine (L1-L4) and total body less head (TBLH) by dual-energy X-ray absorptiometry (DXA) of consecutive pediatric IBD patients. Corresponding data on anthropometry, disease activity and treatment were collected.

Results: 41 patients (age at diagnosis 12.1±3.5 years, 18 males) were included. Mean L1-4 z-score at 1st scan was -1.6±1.0 and TBLH z-score was -1.6±1.0, lower than expected in normal population (p 0.01). L1-4 z-score positively correlated with height-SDS (R=0.44, p 0.01) and weight-SDS (R=0.50, p0.01) and negatively with number of corticosteroids courses (R=-0.31, P=0.05). There was a trend towards improvement of BMD at second DXA scan both in L1-4 Z-scores (-1.4±0.8 vs. -1.6±1.0, p=0.12) and in TBLH z-scores (-1.3±0.9 vs. -1.6±1.0, p=0.08). The change in L1-4 z-scores correlated positively with the change in weight-SDS, height-SDS and BMI-SDS (R=0.55, p0.01, R=0.42, p0.01; R=0.42, p=0.01, respectively). Children with L1-4 z-score ≤-2 at first DXA improved better than children with L1-4 z-score -2 (0.8 vs. -0.1 p0.01). L1-4 z-score of patients≥18 years at second DXA increased significantly compared to younger patients (0.6 vs. -0.1, p=0.02).

Conclusions: BMD correlate with anthropometry and corticosteroids treatment. The improvement in BMD is more pronounced in patients with initial L1-4 z-scoresnd scan.

Poster Presentation (Sunday, April 7, 2019 10:20)

Characterization of a Series of Subjects with Pregnancy and Lactation-associated Osteoporosis (PLaOP) in Israel

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Exceedingly rare, PLaOP presents with vertebral fractures, and entails significant morbidity. The prevalence in Israel is unknown, it is believed to be 2/10,000 in women over the age of 15 in the US.

Aim & Design: A retrospective investigation of a series of 6 patients seen in the last decade. Subjects with transient osteoporosis of the hip were excluded.

Results: Onset of back pain happened 8.2±5.2 weeks after delivery (1-16), in 4 cases after the first pregnancy during lactation, at age 31.8±5.7y. With the exception of one subject, all women breastfed from 6 to 64 weeks, indicating the delay in diagnosis. The number of fractured vertebrae ranged between 2-9. Dietary calcium intake was only 525±82 mg, just one woman had taken vitamin D and calcium supplements during pregnancy. All women were thin, pre-pregnancy BMI was 22.6+2.6 kg/m^2. No other risk factors were identified. When first assessed, the lumbar spine T score was -3.8±0.47, that of the hip -2.05±1.12. Relevant calcium balance biochemical and hormonal parameters were within normal. Four women received teriparatide, 2 bisphosphonates. At last follow-up between 4 and 18 years after presentation, bone density had improved at the spine -2.8±1.0, but not at the hip. Three women had an additional pregnancy, in one case an additional vertebral fracture was documented.

Conclusions: Usually evident after the first delivery, there may be significant delay in the diagnosis of PLaOP. It affects thin women with no apparent major risk factors, has a guarded prognosis, and may recur in subsequent pregnancies.

Poster Presentation (Sunday, April 7, 2019 10:20)

Pseudohypoparathyroidism- A Tale of Hypo and Hypercalcemia with a Genetic Solution

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Introduction: Pseudohypoparathyroidism (PHP) is a rare genetic disease characterized by renal resistance to parathyroid hormone (PTH), presenting with hypocalcemia, hyperphosphatemia and elevated PTH levels. We describe a PHP patient who presented with clinically significant hypercalcemia.

Case description: A 46-year-old woman with a prior history of hypocalcemia presented to the emergency department with new-onset hypercalcemia, renal failure and anemia. She had suffered recurrent hypocalcemic episodes throughout her life with elevated PTH levels and hypocalciuria, suggestive of PHP. Medications included calcium 1800mg/day, alfacalcidol (1α-OHD3) 3mcg/day and cholecalciferol (25-OHD3) intermittently. A previous PTH infusion test supported the diagnosis of PHP. There were no Albright Hereditary Osteodystrophy (AHO) features, other hormone resistances or family history of calcium homeostasis dysregulation. Bearing these characteristics in mind, PHP type 1b seemed most likely and was subsequently proven by genetic testing.

As for the cause of hypercalcemia, Vitamin D intoxication was suspected and supplements stopped with rapid normalization of calcium levels. However, laboratory 25-OHD3 and 1,25-OHD3 levels were surprisingly low. There was no evidence of malignancy. The patient subsequently became hypocalcemic and supplements recommenced at lower doses. The patient remains normocalcemic since.

Discussion: Treatment modalities in PHP include calcium and hydroxylated vitamin D supplements with the aim of maintaining normocalcemia and normalizing PTH levels. Hypercalcemia has been reported rarely in PHP, but frequently in hypoparathyroidism due to vitamin D intoxication. We speculate that our patient`s hypercalcemia was caused by alfacalcidol overdose despite low laboratory 1,25OHD levels. Close surveillance is essential in PHP to prevent potentially life-threatening electrolyte disturbances.

Poster Presentation (Sunday, April 7, 2019 10:20)

Prevalence of Diabetes among Children Treated with Growth Hormone in Israel

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Aims To determine the long term risk for diabetes in a cohort of children treated with recombinant human growth hormone (rhGH) in Israel, using data from the Israeli National Diabetes Register (INDR).

Methods Between 1988-2009, 2,513 children were approved for GH treatment. They were assigned to one of the following two groups. The first group included children treated for isolated GH deficiency (IGHD) and small for gestational age (SGA) and the second included those treated for multiple pituitary hormone deficiency (MPHD), chronic renal failure (CRF), Turner syndrome (TS) and Prader-Willi syndrome (PWS). This cohort was cross linked with the INDR for 2014 (mean follow-up duration was 12.1±5.3 years), and prevalent cases of diabetes were identified. Standardized prevalence ratios (SPR`s) of diabetes were calculated for the 10-29 year age group.

Results In 2014, a total of 23 individuals were identified with diabetes (of them 4 with pre-existing diabetes and 12 with diabetes after cessation of GH treatment). In the IGHD and SGA group 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 group which included MPHD, CRF, TS and PWS there was a significantly higher diabetes prevalence (SPR, 11.94, 95%CI: 6.53-20.00) compared to the general population.

Conclusions No difference in diabetes prevalence was found in the IGHD and SGA groups, compared to the general population. Children treated with GH with pre-existing risk factors have an increased prevalence of diabetes. It is advised to closely monitor blood glucose level during and after GH treatment, especially in those children.

Poster Presentation (Sunday, April 7, 2019 10:20)

Connexin-43 Mediated Cell-cell Communication and Propagation of Adipose Tissue ER Stress in Obesity

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Obesity, a leading global health burden, is a major contributor to type-2 diabetes mellitus. Cellular dysfunction of the obese adipocytes has been shown as an important pathophysiological link between obesity and the development of insulin resistance and diabetes. The obese adipose tissue is characterized by chronic inflammation and cellular stresses such as endoplasmic-reticulum (ER) stress. However, the adaptive or maladaptive response to these cellular insults at the tissue level is less well understood. Increased gap junction (GJ) activity, primarily composed of Connexin-(Cx)43, has been shown to play a pivotal role in the tissue response to various chronic stress conditions. We observed that ER-stress can cross from `stressed` (or 'donor') cells to unstressed ('recipient') cells via Cx43-mediated GJ communication, and ER-stress induction increased GJ function *in-vitro*. In a diet-induced obesity mouse model we demonstrated an increase in Cx43 expression in the intact adipose tissue, which could be primarily attributed to increased Cx43 expression in adipocytes. Moreover, in a preliminary study conducted in high fat diet-fed adipocyte-specific Cx43 knock-out mice, we observed lower fasting glucose levels and improved insulin sensitivity as compared to Cx43 wild type mice, independent of body weight.

Our results suggest that in obesity, adipocyte Cx43 plays a role in the development of adipose tissue dysfunction and consequential impairment of systemic metabolic homeostasis, and may imply Cx43 as a novel therapeutic target for obesity associated metabolic abnormalities.

Poster Presentation (Sunday, April 7, 2019 10:20)

High Risk For Diabetic Foot Ulcer among Hospitalized Patients.

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Aim: Diabetic foot ulcer (DFU) which is commonly preceded by Loss of protective sensation (LOPS) is one of the most fearsome/serious diabetic complications and the leading cause of foot amputation in T2D patients. However, the prevalence of high risk state of DFU in these patients is unknown.

Methods: To estimate the presence of LOPS among hospitalized diabetes patients in internal wards in Assaf-Harofeh-Medical-Center, vibration perception and 10-g monofilament tests were done. Patients with foot ulcer or status post amputation were excluded.

Results*:* A total of 305 patients were tested. 165(54.1%) males and 140(45.9%) females. mean age was 70.3±12.2 years old. The mean duration of diabetes was 12 years (IQR 6-20). Mean HBA1C was 6.8 (IQR 6.15-7.98). 79(25.9%) patients had known retinopathy and 68(22.3%) had known nephropathy. 150(49.1%) had LOPS (either abnormal monofilament test or vibration test or both). Patients with LOPS tend to be older 72.1±11.8 vs. 68.6±12.6 years old, p=0.005 (95%CI 0.53-0.657), had higher creatinine, 1.45±1.1 vs. 1.38±1.4, p=0.02 (95%CI 0.513-0.641), lower albumin, 35.3±5.1 vs. 36.9±4.7, p=0.014 (95%CI 0.518-0.647), lower hemoglobin, 11.5±2.3 vs. 12.3±2.3, p=0.006 (95%CI 0.527-0.655) and compelling significant higher RDW, 16.2±2.1 vs. 15.3±2.2, 0

Conclusions: Half of the diabetic patients in internal wards have unrecognized LOPS, the leading cause for DFU. This window of opportunity should be used to recognize LOPS and take measures for DFU prevention.

Poster Presentation (Sunday, April 7, 2019 10:20)

Familial clinical heterogeneity manifested by the presence of either diabetes or deafness in a pedigree of a patient with Maternally Inherited Diabetes Mellitus and Deafness

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Introduction: Mitochondrial DNA mutation is a rare cause for diabetes mellitus (DM) and deafness that is often misdiagnosed as type 1 or type 2 DM.

Proband: a 25 year-old female presented with a fasting glucose 205 mg/dl, Hb A1c 8.5%. She has been previously diagnosed with sensorineural hearing loss. The family history was notable for several relatives with either diabetes or deafness. Autoimmune diabetes was ruled out. She responded well to basal insulin treatment, with an achieved Hb A1c of 7%. Her genetic workup identified a mutation in the mitochondrial DNA m.3243AG which is associated with MIDD (maternally inherited diabetes and deafness) and MELAS (mitochondrial encephalopathy, lactic acidosis and stroke like episodes). The following specific recommendations were made, which differ from the standard practice and guidelines in the care of classical type 1 or type 2 diabetes: 1) avoid metformin; 2) rigidly maintain adequate carbohydrate consumption when ill, as stroke- like episodes have been described in this condition during acute illness when carbohydrate supply was inadequate; 3) use Coenzyme Q10 which might enhance insulin secretion and potentially improve symptoms of myopathy. 4) attempt not to postpone fertility due to the risk of premature ovarian failure; 5) for pregnancy planning, consider "three parent IVF" with mitochondria and cytoplasm from a donated ovum, thus potentially avoiding transmitting the defect.

Conclusion: Diagnosis of MIDD should be considered in subjects with family history of premature deafness and diabetes, not necessarily in the same subjects. The correct diagnosis may offer multiple therapeutic advantages.

Poster Presentation (Sunday, April 7, 2019 10:20)

Towards Implementation of St. Vincent Declaration – Outcomes of Pre-gestational Diabetic Women Pregnancies

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Introduction: pre-gestational diabetes mellitus (PGDM) carries a significantly elevated risk of adverse maternal and fetal outcomes. There is evidence that certain interventions reduce the risk for adverse outcomes. Studies show that a multi-disciplinary approach improves pregnancy outcomes in PGDM women.

Aims: to report pregnancy outcomes using a multi-disciplinary approach and to compare pregnancy complications rates in this Pre-pregnancy Diabetes Cohort Study (PDCS) to rates reported in the literature.

Methods: This was a historical prospective study which included all consecutive women with pre-gestational type 1 and type 2 diabetes mellitus that were monitored before and/or during pregnancy at the high-risk pregnancy clinic at the Sheba medical center.

Results: 121 neonates from 116 pregnancies of 94 women were included in the analyses. In 83% of the pregnancies continuous glucose monitoring (CGM) sensors were used during the whole pregnancy or part of it. Pregnancy outcomes amongst women that were followed by a multi-disciplinary team before, frequently during pregnancy and during labor and puerperium resulted in better glucose control (6.4% vs 7.8%), a lower risk for pregnancy induced hypertension(PIH)/preeclampsia (7.7% vs 15.6%), lower birth weight (3212gr vs 3684gr) and a lower rate of LGA and macrosomia (23.1% vs 54.2%, 3.3% vs 28.4% respectively), compared to data from European cohorts.

Conclusions: the multi-disciplinary approach for treating PGDM women practiced in the high-risk pregnancy clinic at the Sheba Medical Center resulted in lower rates of macrosomia, LGA and PIH compared to what is reported in the literature.

Poster Presentation (Sunday, April 7, 2019 10:20)

Diurnality, Type 2 Diabetes, and Depressive-like Behavior

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Although type 2 diabetes (T2DM) and depression are associated with disturbances of circadian rhythms, most studies of these diseases use nocturnal mice and rats while modeling diurnal humans. We suggest that the development of T2DM and depression is related to changes which accompanied the switch from the mammalian ancestral nocturnal activity to the current diurnal one. We show that diurnal sand rats (*Psammomys obesus*) held outdoors in laboratory cages (where they are exposed to natural environmental conditions) and fed standard rodent diet do not develop T2DM in contrast to animals held indoors (where the only cycling environmental condition is light) fed the same diet. Moreover, keeping sand rats under short photoperiod dampened behavioral and molecular daily rhythms, resulted in anxiety- and depressive-like behavior, and accelerated the development of T2DM. We suggest that the disturbed rhythms disrupt the internal temporal order and metabolic pathways controlled by feeding and the circadian system, resulting in the development of T2DM and depressive like behavior. We further suggest that using nocturnal mice and rats as sole model animal may limit research, especially when studying circadian rhythm-related diseases.

Poster Presentation (Sunday, April 7, 2019 10:20)

Hospital discharge of diabetic patients and fulfillment recommendations

for the diabetes management in outpatient therapy.

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OBJECTIVE

Effective treatment algorithms are needed to guide diabetes care at hospital

discharge in internal medicine departments for patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This retrospective study aimed to determine the efficacy of recommendations for diabetes treatment during discharge from hospital . All patients during hospitalization were treated with basal –bolus insulin regiment. The primary outcome was HbA1c level at 12-16 weeks after hospital discharge. The secondary outcome was to access diabetes control after 6-9 and 12-15 month after discharge.

RESULTS

A total of 140 patients with type 2 diabetes , on basal bolus insulin regiment during hospitalization were included in the statistical analysis. 72 patients (51%)discharged on basal bolus protocol,55 patient (39%) discharged on their home management , 10 patients(7%) added short or long acting insulin on their home treatment, and in 3 patients(2%) oral treatment was changed.

The preadmission HbA1c was 9.5% in basal –bolus group, and decreased to 8.5 at 12-14 weeks of follow-up (P = 0.07). After 5-9 month of treatment basal bolus group has A1C level of 9% vs 9.5% of preadmission level , and after 12-15 month it was 8.9% . (p=0.05).In the group with any change in previous treatment A1C decreased from 9% to 7.7% and after 12-15 month after discharge A1C level was 8% . In the group with no changes in diabetes treatment on discharge no significant changes in A1C level was observed (8.6% vs 8.5%) throughout all period of observation (figure 1).

CONCLUSIONS

Diabetes transitional care from inpatient to outpatient and proper recommendations for diabetic patients during discharge from hospital can improve long term diabetes control.

Poster Presentation (Sunday, April 7, 2019 10:20)

The Role of the Adipokine FABP4 in the Pathophysiology of Gestational Diabetes

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Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy, defined by hyperglycemia and insulin resistance during pregnancy. GDM is of great concern given the serious health consequences for both the mother and the offspring. Fatty acid-binding protein 4 (FABP4) is one of the most abundant proteins in mature adipocytes, and has been identified as an active adipokine modulating glucose homeostasis by promoting hepatic glucose production. Of interest, increased levels of FABP4 has been demonstrated in GDM, however its differential contribution to its pathophysiology is unclear.

Our preliminary results, in accordance with other studies, indicate significantly higher circulating levels of FABP4 in women with GDM (n=14) vs. normoglycemic pregnant women (n=55); median FABP4 levels are 20.1, IQR 14.6-22.6 ng/ml and 10.0, IQR: 7.8-13.9 ng/ml respectively, p=0.01.

In order to identify the source of elevated circulating levels of FABP4 in GDM, we collected both subcutaneous and visceral white adipose tissue (WAT) biopsies as well as placenta samples from 17 women with GDM and 19 normoglycemic pregnant woman, aged 37.5±4.6 and 36.6±5.4 years with a BMI of 29±10.1 and 24.9±6.1 kg/m^2, respectively. The results demonstrate that both adipose tissues and placenta express and secrete FABP4. Yet, there was a differential increase in FABP4 secretion from visceral WAT of GDM women compared to normoglycemic pregnant women, likely representing the source of elevated serum FABP4 in GDM.

This study highlights the importance of the visceral adipose tissue and FABP4 as potential contributing factors to the pathophysiology of insulin resistance in GDM.

Poster Presentation (Sunday, April 7, 2019 10:20)

The Association between Glycemic Control and Mortality- A Retrospective Cohort Study

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Introduction

Among patients with diabetes mellitus (DM), both low and high levels of glycemic control, as well as variability of HbA_{1c} over time, were shown to be associated with an increased mortality risk.

Aim

To investigate the association between glycemic control and mortality in a cohort of diabetic patients.

Methods

This retrospective cohort study included all patients aged 50 years and older with diagnosis of DM or HbA1c measurement ≥6.5%, between 2001-2016 from the Southern region of Israel, and who are registered with Clalit Health Services. Eligible patients were followed up to January 2018 for the primary outcome, all-cause mortality. Association between the mean HbA1c in the last year of follow-up and mortality was analyzed using logistic regression.

Results

Our cohort consisted of 51381 diabetic patients (47% males), of whom 13669 (26.6%) died during the observation period. The data showed a statistically significant (p values0.0001) positive association between mortality risk and elevated HbA1c values. The adjusted odds ratio (OR) for mortality was 0.342 (0.314-0.373) for HbA1c6.5%, 1.969 (1.833-2.115) for 7.5%≤HbA1c8.5%, 3.612 (3.311-3.941) for 8.5%≤HbA1c9.5%, and 16.457 (15.012-18.041) for HbA1c≥9.5%, compared with 6.5%≤HbA1c7.5% (reference range). We adjusted for gender, age, glycemic variability as COV (coefficient of variation) and disease duration.

Conclusion

Worse glycemic control was exponentially associated with an increased mortality risk.

Poster Presentation (Sunday, April 7, 2019 10:20)

Heterozygous RFX6 Mutation as a Cause of Diabetes Mellitus in a Multigenerational Family

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Background: Monogenic diabetes mellitus (DM) is an early-onset, non- autoimmune diabetes. Genetic diagnosis can personalize patient management and lead to prevention. We describe four generations of DM in one family, caused by a heterozygous mutation in the *RFX6* gene. RFX6 (Regulatory factor X, 6) is essential for the development of the endocrine pancreas. Mutations in *RFX6* can cause neonatal (Mitchell-Riley syndrome) as well as childhood DM, intestinal atresia and hepatobiliary abnormalities.

Patients and methods: Transient, stress hyperglycemia was the first clinical presentation of our patient at the age of 3 years. Non-autoimmune DM was diagnosed at 13 years. Maternal family history revealed great-grandmother, grandmother and a mother, two aunts and one cousin with DM. They were diagnosed as diabetics in adolescence or young adulthood. Only the patient`s mother was treated with insulin.

Next generation panel sequencing for genes of monogenic DM, using the Trusight One platform (Illumina), was utilized for genetic analysis of the proband. Sanger sequencing was performed to validate the likely-pathogenic finding and for segregation analysis in the family.

Results: We identified a heterozygous mutation in *RFX6* gene (c.781-2_787delinsG affecting intron7/exon 8) in the proband that co-segregated in five family members with DM, and in the patient`s healthy brother. One uncle who carries the mutation has asymptomatic DM. This mutation was previously reported to cause autosomal recessive neonatal diabetes.

Conclusions: Heterozygous *RFX6* mutation was diagnosed as the cause of familial DM. Genetic evaluation of youth with non – autoimmune DM provides accurate diagnosis and identifies subjects at risk.

Poster Presentation (Sunday, April 7, 2019 10:20)

Outcomes of Community-acquired Sepsis in Patients with Diabetes: A Retrospective Population-based Cohort Study.

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Introduction: Patients with diabetes mellitus (DM) experience increased risk for community acquired sepsis. However, the prognostic influence of diabetes on sepsis outcomes remains unclear.

Aim: To evaluate sepsis outcomes in patients with and without DM.

Methods: We conducted a retrospective study, based on data collected from medical files. The study included adult patients hospitalized at the Assaf Harofeh medical center, from August -December 2016. Hazard ratios (HRs, Cox regression) and odds ratios (ORs, logistic regression) were calculated for the association between DM and sepsis outcomes. Multivariable regression and regression stratified by propensity score quintiles (PS) were used to adjust for potential confounders.

Results: Among 1527 patients with community acquired sepsis, 469 (30.7%) had DM. Diabetic patients were older (75 y/o (IQR 66-83) vs 59 y/o (34-78)(p 0.001) had more co-morbidities (Charlson Combined Condition Score 7 (IQR 5-8) vs 2 (0-5) p 0.001), and were exposed to health care facilities more frequently.

HR was 1.285 (0.92-1.794) p=0.141, and 2.002 (1.542-2.599) p 0.001 for mortality during hospitalization and at 90 days, respectively. Adjusted HRs were 1.206 (0.85-1.713) p=0.294 and 1.134 (0.863-1.489) p= 0.366, respectively. OR for functional status deterioration was 1.949 (1.364-2.785)

Conclusion: Patients with DM and community acquired sepsis did not experience worse outcomes than patients without DM.

Poster Presentation (Sunday, April 7, 2019 10:20)

The Relationship between Low Carbohydrate Diet & Pregnancy Outcomes in Women with Pre-Gestational Diabetes- A Historical Prospective Study

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Aim

Among women with pre-gestational diabetes to determine the relationship between a reported lower carbohydrate diet and adverse obstetrical or neonatal outcomes.

Methods

This was a historical prospective study unifying data from hospital records with glucose values collected through the Medtronic CareLink® pro software (Medtronic MiniMed, Northridge, CA). The study included all consecutive women with pre-gestational T1DM and T2DM that were monitored before and/or during pregnancy at the high-risk pregnancy clinic in which data regarding pregnancies and neonates outcomes were available from 2010-2018. The relationship between reported carbohydrate consumption (dichotomized into

Results

This analysis pertains to 145 consecutive deliveries; in which 17.2% reported an average consumption of carbohydrate 45U OR 0.41 (95%CI 0.17-0.99 P=0.048).

Conclusions

In women with pre-gestational diabetes a reported carbohydrate consumption of 45U.

Poster Presentation (Sunday, April 7, 2019 10:20)

New Autosomal Dominant Mutation in Glucokinase Gene Causing Congenital Hyperinsulinism

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Introduction: Autosomal dominant congenital hyperinsulinism (CH) is characterized by congenital hypoglycemia due to mutations in any of several genes including the glucokinase (GCK) gene. It is a rare disease with variable clinical symptoms mostly treated medically but in some cases requiring surgical intervention.

Aim We describe herein the clinical presentation and the genetic diagnosis of CH in a two generations of an Israeli family.

Methods/patients: The proband was a 25 years old male who presented with hypoglycemia (glucose 40 mg/dl normal range70-100). He felt hypoglycemic symptoms from early age but was never treated medically. He served in the army as a combat first aid provider at the field unit. His mother and his brother were found to be hypoglycemic but were never treated medically. His other brother was normoglycemic.

Results: DNA sequencing of GCK gene identified a novel heterozygous missense mutation (p.(Lys459Asn), c.1377GC) in exon 10 in the proband, his mother but not in his normoglycemic brother. Continuous glucose monitoring revealed asymptomatic low glucose levels down to 40 mg/dl (normal range70-100) during day and night.

Conclusion: CH characterized by hypoglycemia due to a mutation in the GCK gene was diagnosed in two generations of an Israeli family. The congenital condition was not treated by medications. Obtaining a detailed personal and family medical history and, when appropriate, performing targeted genetic testing, is critical to correctly diagnose hyperinsulinemic hypoglycemia. Identifying the genetic etiology has important implications regarding medical therapy and follow-up.

Poster Presentation (Sunday, April 7, 2019 10:20)

Antibody-negative Insulin-dependent Diabetes in Two Patients Treated with Immune Checkpoint Blockade

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Introduction

Insulin-dependent "type 1-like" diabetes is an uncommon devastating side effect of PD-1/PD-L1 immunotherapy, with an incidence of 0.4-0.9%. Thus far only a few dozen cases were described, about half without recognizable autoantibodies. All presented with very low to undetectable C-peptide levels with a very rapid onset following PD-1 treatment initiation, some with ketoacidosis. All patients completely dependent on multiple daily insulin injections. The underlying mechanisms and measures to halt or reverse insulin deficiency remain unknown.

Case description

We describe two patients diagnosed with metastatic melanoma. None had diabetes before treatment. PD-1 treatment was initiated and 8-weeks afterward both developed severe insulin-dependent diabetes. One had DKA at presentation and the other ketosis without acidosis. C-peptide levels were extremely low, and antibodies were negative. Both patients died of metastatic melanoma a few months later.

Discussion

The pathogenesis of complete beta-cell destruction within weeks from PD-1 initiation is not well understood. Both our patients and half of the patients described previously were autoantibody negative implying a unique underlying mechanism. PD-L1 is expressed in pancreatic islets and PD-1/PD-L1 seems to play a protective role by inhibiting activation of autoreactive T-cells inducing tolerance.

Conclusion

We describe two patients with fulminant diabetes following initiation of PD-1 treatment. Although uncommon, this serious complication has to be recognized. We emphasize that glucose levels should be routinely screened before of PD-1/PD-L1 treatment initiation and regularly with each course of treatment, especially in the first months. Unfortunately, the underlying mechanisms, predictors and therapeutic measures beside insulin treatment, are still unknown.

Poster Presentation (Sunday, April 7, 2019 10:20)

Atypical Presentation of Type 1 Diabetes Mellitus

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Diabetic ketoacidosis (DKA) is associated with Type 1 diabetes mellitus (T1DM), whilst hyperglycemic hyperosmolar state (HHS) with Type 2 (T2DM). HHS has been well described as a presentation of T1DM in children, but not in adults.

Aim: To present a case of T1DM presenting with HHS.

Methods: Case Report. A 21 year old male presented with a 4-5 day history of weakness, thirst, polydipsia and polyuria. He had vomited once. He was previously well but had received Growth Hormone for idiopathic short stature at age 15-18. He has a cousin with T1DM.

Results: On examination he was afebrile, pulse 62, BP 125/57, BMI 22. Blood glucose was 993, Na 131, K 5.2, creatinine 1.2, pH 7.353, bicarbonate 23.5, serum osmolality 319. Anion gap not measured. Urine ketones 15. HbA1c 10.2%. In view of his age he was treated as for DKA with intravenous fluids and insulin. He displayed substantial insulin resistance and at discharged required a total of 82U daily, . Over the subsequent weeks his insulin requirement fell to 24U daily two months after discharge. Serological studies showed positive anti-GAD and anti-islet cell antibodies at over 2000 [5] and over 900 [30] respectively.

Conclusions: This patient presented with a picture typical for HHS in T2DM, apart from his young age. In spite of his normal weight he exhibited severe insulin resistance presumably as a result of glucotoxicity, but with sufficient residual insulin secretion to prevent ketoacidosis. Whether there is an association with his previous GH treatment is unknown.

Poster Presentation (Sunday, April 7, 2019 10:20)

Insulin Treatment is Associated with Improved Fetal Placental Vascular Circulation in Obese and Non Obese Women with Gestational Diabetes Mellitus.

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Objective: The present study was designed to investigate the impact of carbohydrate restriction and insulin treatment on placental maternal and fetal vascular circulation in obese and non-obese women with gestational diabetes mellitus (GDM).

Design and methods: 192 women with GDM who gave birth and underwent a placental histopathological examination at Wolfson Medical Center, Israel were included in the study: 123 women who were treated with carbohydrate/calorie restriction diet (Group 1) and 69 women who were treated with diet plus insulin (Group 2). Additionally, each group was divided into two subgroups according to pre-pregnancy BMI: non-obese and obese.

Results: Maternal vascular malperfusion lesions did not differ significantly between groups. Vascular lesions related to fetal malperfusion were significantly lower in GDM women treated by insulin and diet compared to women with diet alone (p=0.027). Among fetal malperfusion lesions, villous changes consistent with fetal thrombo-occlusive disease (FTOD) were significantly lower in women treated with diet plus insulin and lowest in GDM women with prepregnancy BMI

Conclusion: Combination of obesity and GDM increased rate of FTOD and prevalence of gestational hypertension. Carbohydrate restriction diet plus insulin treatment was associated with improved fetal placental vascular circulation, especially in GDM women with prepregnancy BMI 30.

Poster Presentation (Sunday, April 7, 2019 10:20)

The Association Between Obesity and Secular Trend of Stature: A Nationwide Study of 2.8 Million Adolescents over Five Decades.

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Background: It is unclear whether adolescence obesity is associated with limited linear growth. We assessed this association in a nationwide cohort of adolescents.

Methods: We conducted a nationwide, population-based, cohort study of 2 785 227 Israeli adolescents (60% males) who were examined before military service in 1967 through 2015; Height and weight were measured along with assessment of medical status at age 17.4±0.4 years. The secular trend of height was plotted for US-CDC age- and sex-adjusted BMI percentiles groups. We accounted for health status at enrollment and computed the expected height based on parental data that was available for 512 978 examinees.

Results: Mean height has increased by 3.1 cm among males, but remained unchanged among females over five decades. Among males, gain in height was mostly attained during the first 25 years and has stabled since. Obese males were taller than their normal-weight and underweight counterparts. Underweight girls had a prominent increase in mean height during the first 2 decades exceeding by over 2 cm the mean height of their obese counterparts. There was a gradual decrease in the difference between measured and expected height in males and females regardless of BMI status, with the exception of underweight females who achieved consistently higher stature than expected (≥3 cm).

Conclusions: During five decades excessive BMI was not a limiting factor in growth potential compared to normal BMI in both sexes. Underweight females with unimpaired health are the sole group that has yet realized its growth potential even when accounting parental height.

Poster Presentation (Sunday, April 7, 2019 10:20)

Identification of ZYG11A as a Novel 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 (GHR) mutations, leading to congenital insulin-like growth factor-1 (IGF1) deficiency. Epidemiological studies have shown that LS patients are protected from cancer. The Zyg-11 family member-A (ZYG11A) gene, a potential cell cycle regulator, has been shown in genomic analyses to be upregulated by 3-fold in LS patients compared to healthy controls. ZYG11A has not been previously linked to IGF1 signaling and it's involvement in endometrial cancer is unknown.
Aim: The overall goal of this project was to elucidate the potential role of ZYG11A in endometrial cancer. Specifically, our aim was (1) to assess the regulation of ZYG11A by IGF1 and INS, and (2) to evaluate the impact of p53 mutational status on ZYG11A regulation and function.
Methods: Uterine serous papillary endometrial carcinoma-derived cell lines (USPC1 and USPC2) were used in this study. Quantitative Real time PCR (qRT-PCR) and Western immunoblotting were carried out following IGF1/INS treatments. Knockdown studies were conducted using siRNA technology.
Results: Experiments revealed that treatment with IGF1 or INS resulted in reduction in ZYG11A expression levels in USPC1 cells (expressing a wild-type p53), whereas they stimulated ZYG11A levels in USPC2 cells (expressing a mutated p53). ZYG11A silencing had a negative effect on cell proliferation, enhanced apoptosis and affected expression of cell cycle-regulated genes.
Conclusions: In conclusion, our study provides evidence that ZYG11A constitutes a new target for GH-IGF1 action. Future studies will address the biological role and mechanisms of action of ZYG11A.

Poster Presentation (Sunday, April 7, 2019 10:20)

Is There a Correlation Between miRNA hsa-132-3p Expression and Longevity in Laron Syndrome Patients?

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Background: Laron Syndrome (LS), or primary growth hormone (GH) insensitivity, is a genetic disorder that is transmitted by autosomal inheritance. LS is caused by mutations in the GH receptor (GHR) gene, or by post-receptor defects, leading to a defective GH signaling pathway. Recent epidemiological studies have shown that LS patients are protected from cancer. Furthermore, mouse models of LS display an approximately 50% increase in lifespan. MicroRNAs (miRNAs) are short non-coding RNAs that regulate the expression of complementary mRNAs. miRNA hsa-132-3p is an RNA molecule that is involved in a wide variety of cellular processes. To investigate differentially regulated miRNAs in LS patients compared to healthy controls, our laboratory has recently conducted genome wide association studies.

Aim: The aim of the present study was to investigate: (1) the potential regulation of miRNA hsa-132-3p expression by IGF1; and (2) the putative correlation between high expression of miRNA hsa-132-3p and longevity in LS-derived cells *in vitro*.

Methods: LS patient-derived lymphoblastoid cells and human embryonic kidney 293 (HEK293) cells were used. Microarray analysis, Affymetrix GeneChips Microarray RNA assays and Quantitative Real time PCR (qRT-PCR) were carried out. miRNA silencing experiments were performed.

Results: Among the miRNAs shown to be differentially expressed in LS patients, we identified miRNAs hsa-132-3p as a highly up-regulated miRNA in patients. These results were validated by qRT-PCR. Ongoing silencing experiments will elucidate the effect of miRNA hsa-132-3p on cellular senescence.

Conclusions: Our study provides preliminary evidence for a correlation between miRNA hsa-132-3p expression and senescence in LS patients.

Poster Presentation (Sunday, April 7, 2019 10:20)

Treatment Landscape for active Acromegaly in a Pituitary Centre in Israel

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Introduction: Active acromegaly is associated with increased morbidity and mortality. At least 50% of patients with acromegaly require medical treatment. Options for treatment include somatostatin analogues (SSA; octreotide, lanreotide), pegvisomant, pasireotide, cabergoline, or combination treatment. Radiotherapy may be offered in some cases.

Aim: To report the real-life experience with medical treatment for acromegaly in a large cohort.

Methods: Data on demographic parameters, blood tests results, imaging studies and treatments was extracted from 87 patients records.

Results: Our cohort includes 87 patients (43 males) with active acromegaly. Mean age at diagnosis, 40±11years, mean follow up, 8 years. 70 patients presented with a macroadenoma, and mean baseline IGF-1 was 3.2±1.9 XULN; 75 patients underwent surgery, and 13 received radiotherapy. Currently, 36 subjects receive SSA, pegvisomant – 10, pasireotide -17, cabegoline- 4, estrogen- 2 females, SSA combined with pegvisomat - 10, and pegvisomant combined with pasireotide -1. Seven patients are not actively treated, including 4 following radiotherapy. Good biochemical control was achieved in 75 patients (86%), and 12 patients (14%) are currently uncontrolled. 80% of controlled patients are treated by one medication; 16% are on combination therapy and the rest received radiation therapy. Adverse events included diabetes in 7 patients on pasireotide, and 4 others with symptomatic cholelithiasis.

Conclusions: Active acromegaly can be controlled medically in most patients with the currently available drugs, either as monotherapy or a combination treatment, with low rate of adverse effect. This cohort displays the variety of medical treatment options available for treating acromegaly.

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Poster Presentation (Sunday, April 7, 2019 10:20)

Poster

Growth - GH/IGF/Growth factors

Patients with Congenital IGF-1 Deficiency Have an Abnormal Plasma Amino Acid Pattern Partially Reversed by IGF-1 Treatment

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Background: Laron syndrome (LS), (OMIM#262500) is a rare recessively inherited disease caused by deletions or mutations of the GH receptor, and is characterized by low or undetectable serum IGF-I. This deficiency leads to a series of metabolic abnormalities including of the proteins and affects muscular mass and body composition.

Subjects & Method: We studied 8, amino-acid analysis of 3 untreated, 2 IGF-1 treated LS patients and 3 heterozygote family members. 1 healthy brother, 2 young females, and 3 old aged subjects. We used the LC-MS/MS method to separate and measure the amino acids levels (Waters TQS Micro system).

Results: The main findings are summarized in the following Table:

Subjects	Sar	Cit	Lys244	Orn	Tau
LS IGF-I -	↑	↓	↑	↑	Normal
LS IGF-I +	Normal	Normal	↑↑	↑	Normal
Heterozygote	↑	↓	Normal	Normal	Normal
Age>80y (2F,1M)	↑	Normal	Normal	Normal	Normal
Turner, PCOS	Normal	Normal	Normal	Normal	Normal
Healthy Control	Normal	Normal	Normal	Normal	Normal

Sar=Sarcosine, Cit=Citrulline, Lys=Lysine, Orn=Ornithine, Tau=Taurine.

The IGF-1 values of the untreated LS patients were much lower than those of the controls. It is evident that IGF-1 deficiency increases plasma ornithine, lysine and sarcosine and lowers citrulline. IGF-1 replacement treatment increase the levels of Lysine and Ornithine compared to the control.

Conclusions: This is the first report that congenital IGF-I deficiency alters the plasma amino acid composition which is partially reversible by long term IGF-I replacement therapy.

Poster Presentation (Sunday, April 7, 2019 10:20)

The Second to Fourth Digit Ratio in Patients with Congenital Igf-1 Deficiency

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Introduction: The relationship between the length of the second and fourth index finger (2D:4D ratio) is a sexually dimorphic trait, higher in females than in males. It is established during early prenatal development under the influence of sex hormones, as demonstrated in numerous studies both in humans and in mice.

Aim: To measure the 2D/4D ration in patients with congenital isolated GH deficiency (cIGHD) and Laron Syndrome (LS).

Methods: Measurements were made from 78, left hand x-rays of 31 patients 16 LS, 9 cIGHD and 9 heterozygote family numbers, 7 patients had repeated x-rays. Mean bone age (BA) was 11.2 ± 6.6yrs. As control served age adjusted BA x-rays from the Greulich & Pyle Atlas.

Results: There was no difference between the 2 genders of the patients denoting loss of sexual dimorphism. Further results are summarized in the Table.

X-ray	Mean Bone Age	2D:4D ratio		p-value
		Patient	Control	
1st x-ray (N=7)	5.26 ± 4.13	0.933 ± 0.031	0.898 ± 0.024	0.09
2nd x-ray (N=7)	12.82 ± 2.24	0.951 ± 0.023	0.904 ± 0.025	**0.005**
p-value	**0.003**	**0.013**		

With advancing age the 2D:4D ratio in the patients + heterozygotes increased significantly; the patients having a higher 2D:4D ratio than the controls denoting a feminization pattern.

Conclusion: Congenital IGF-I deficiency has an intrauterine effect on digit growth.

Poster Presentation (Sunday, April 7, 2019 10:20)

Combined Autophagy and mTOR Inhibition Reduces Cells Proliferation and Induces Apoptosis in a Lung Carcinoid In-Vitro Model

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Background: Treatment options for patients with metastatic lung carcinoids (LC) are limited. Everolimus (RAD001), an mTOR inhibitor (mTORi) which suppresses tumor cells growth & proliferation, appears to be efficient in these patients; however, it promotes autophagy, thereby paradoxically supporting tumor cell survival and development of drug-resistance. We have previously demonstrated in a BON-1 pancreatic NEN model that adding chloroquine (CQ, an autophagy inhibitor) to mTORi markedly inhibited cell proliferation and induced apoptosis compared to mTORi alone.

Aim: To investigate the effect of CQ ± mTORi on LC cell viability, proliferation and apoptosis.

Methods: The LC cell line NCI-H727 was treated with CQ, RAD001 and Torin1, alone or in combination. Cell viability and proliferation were examined by XTT and Ki67 staining. Flow cytometry and Western blot were used to assess drug effects on cell cycle, apoptosis, PI3K/Akt/mTOR and autophagy pathways. The effect of differential timing of drug administration was examined by using a cytotoxicity kit.

Results: CQ alone reduced LC cell viability by ~ 30%; the addition of CQ to RAD001 or Torin1 significantly reduced cell viability by 60% and 98%, respectively. Moreover, Torin1 or RAD001 combined with CQ induced a higher degree of apoptosis and accumulation of LC3-II (a marker of autophagy).

Conclusion: In the present *in-vitro* LC model, CQ alone and mainly in addition to a mTORi, promotes apoptosis and suppresses cell proliferation, potentiating the effect of mTORi. Further experiments are needed to understand the role of CQ in the treatment arsenal of patients with metastatic LC.

Poster Presentation (Sunday, April 7, 2019 10:20)

Distinct Activities of IGF1R and INSR on ERK and AKT Signaling Pathways in Breast Cancer Cells

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Introduction: Breast cancer development and progression are influenced by insulin-like growth factor-1 (IGF1R) and insulin (INSR) receptor signaling, which drive typical cancer phenotypes such as cell growth, proliferation, and migration. However, it is still unknown why IGF1R and INSR, despite the fact that they share most of their downstream cytoplasmic signaling mediators, exhibit, for the most part, distinct, well-defined functions.

Aim: To evaluate the specific impact of IGF1R and INSR on ERK and AKT pathways in breast cancer-derived cell lines.

Methods: MCF7-derived stable cell lines lacking IGF1R or INSR expression (IGF1R-KD, INSR-KD) were employed in the current research. The expression and activation of specific downstream genes involved in IGF1 and insulin signaling was assessed by Western blots. IGF1R promoter activity was measured by luciferase assays. Proliferation was evaluated by XTT assays.

Results: Western blotting analyses showed that IGF1R silencing had a major impact on nuclear ERK1/2 and AKT activation. Promoter measurements indicate that ERK2 and AKT stimulated IGF1R promoter activity, although this effect was markedly reduced in IGF1R-KD and INSR-KD cells.

Conclusions: Our results indicate that insulin and IGF1 pathways have different effects on the subcellular distribution (and, particularly, the nuclear presence) of ERK1/2 and AKT molecules. Both cytoplasmic mediators are capable of binding and transactivating the IGF1R promoter. Our data is consistent with the notion that, in addition to their classical role as targets for insulin-like molecules, both ERK1/2 and AKT are involved in transcriptional control of the IGF1R gene.

Poster Presentation (Sunday, April 7, 2019 10:20)

Two Distinct Cyp19a1 Gene Promoters are Utilized Differently in Ovary and Hypothalamus for Driving Expression of Aromatase

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The *cyp19A1* gene encodes aromatase, a key enzyme in estrogen biosynthesis, which catalyzes the conversion of androgens to estrogens. The *cyp19A1* mRNA appears as a number of different isoforms in various tissues as a result of different transcriptional start sites (TSSs) and alternative splicing, indicating that distinct regulatory regions are utilized in the various tissues. The aim of this study was to determine the isoforms of *cyp19a1* in the hypothalamus and ovary, to begin to characterize the regulatory elements (promoters and enhancers) driving their expression, and to determine how this relates to their relative expression levels. After extraction of RNA from mouse hypothalami and ovaries, we carried out RT- real time PCR, RT-PCR and 5` RACE (5` Rapid amplification of cDNA ends), which lead to the identification of two distinct TSSs located 30 kbp apart, both of which appear functional in both tissues. However, the downstream TSS is utilized preferentially in the ovary and directs transcription of a first exon that serves as the 5'UTR in this ovarian-predominant isoform. The isoform expressed from the more upstream TSS is found in the brain at similar levels as the isoform which is predominant in the ovary, and contains a different 5'UTR, while both transcripts encode the same protein. Identification of these two distinct TSSs points to promoters that are utilized differently in these tissues and enables further study of the mechanisms of their activation, and also for understanding the reasons for miss-expression of this gene in certain pathological conditions.

Poster Presentation (Sunday, April 7, 2019 10:20)

Pregnancy in 17 Hydroxylase Deficiency

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Introduction: Mutations that selectively ablate 17,20-lyase are exceedingly rare and belong to the rarest steroidogenetic disorders. An E305G mutation in the active site of CYP17A1 causes isolated 17,20-lyase deficiency. Only three patients with 17a-hydroxylase deficiency have successfully delivered offsprings, none in an isolated 17,20-lyase deficiency. **Methods:** A 24yo, infertile patient with 17-hydroxylase deficiency has undergone an IVF cycle, downregulated with the long GnRH agonist protocol, 30 mg of prednisone daily, and menopausal gonadotropins. 36 hours after hCG, 37 oocytes were retrieved and after ICSI, 25 ova fertilized, and 17 cryopreserved. In a subsequent cycle, the endometrium was stimulated with estradiol, under progesterone suppression with long acting GnRH agonist and high dose prednisone. When endometrial width of 8.5 mm was reached, vaginal progesterone was added, and on the fourth day, two embrya were thawed and transferred to the endometrial cavity. **Results:** Despite 11 days of human menopausal gonadotropin administration, the estradiol concentrations were low, but the progesterone remained high (10-38 nmol/L), therefore, no fresh embryo transfer was carried out and all embryos were cryopreserved. Twelve days after thawed embryo transfer, hCG was 105 U/L, and a week later an intrauterine gestational sac was detected. Unfortunately, this pregnancy ended in missed abortion, and another ET attempt is planned. **Conclusion:** Pregnancy can be achieved in patients with 17-hydroxylase deficiency, by IVF, freezing all generated embrya, and ET in a subsequent cycle, while suppressing endogenous ovarian progesterone with a GnRH agonist and adrenal suppression with high dose prednisone.

Poster Presentation (Sunday, April 7, 2019 10:20)

RNA-Seq Analysis of Ovariectomy-Induced Changes in Mouse Liver Reveals New Targets for Menopause-Associated Metabolic Derangement

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Menopause is associated with adverse metabolic changes and increased cardiovascular risk profile. **Aim:** To discover differently expressed genes in ovariectomized (OVX) mouse livers and after 17-β-estradiol treatment. **Methods:** Five groups of 9-week-old C57BL/6J female mice (10 per-group) underwent ovariectomy/sham operation and left untreated for 6-weeks to develop metabolic changes. Two groups were sacrificed, and livers harvested. Remaining groups were treated with E2/vehicle for 6-weeks then sacrificed. RNA-seq was performed on liver samples 6 weeks post-surgery. **Results:** OVX mice exhibited significant weight gain. 103 genes (35 up; 68 down) were differently expressed (fold-change ≥2, P ≤0.05, max count ≥30) between groups at 6-weeks post-surgery. OVX mice showed upregulation of gene sets for: fatty acid metabolism, oxidative phosphorylation, myc targets, peroxisome, adipogenesis, androgen response, UV response and TNF-α signaling via NF-Kβ. Downregulated gene sets included: mitotic spindle and G2M checkpoint. Specific differently expressed genes were validated an analyzed using real-time PCR at 6- and 12-weeks post-surgery with/without E2 treatment. Surprisingly, ENHO, encodes for Adropin, a recently described regulator of fat metabolism, associated with cardiovascular health, was decreased at 6-weeks (fold change -2.1, p=7.2e-9) and 12-weeks after OVX (-1.42, p=0.008), though wasn't changed following E2 treatment. Importantly, reduced ENHO expression was found in cardiomyocytes 12 weeks post-surgery (relative mRNA expression=0.44, P=0.03). **Conclusions:** Our results show ovariectomy has a unique transcriptional effect on liver gene sets for metabolism and inflammation. The role of Adropin as a biomarker and a possible therapeutic target in menopause-associated metabolic derangement remains to be investigated.

Poster Presentation (Sunday, April 7, 2019 10:20)

Factor Predicting Survival of Patients with Distant Metastasis (DM) Medullary Thyroid carcinoma

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Introduction: The clinical course of metastatic MTC varies from an extremely indolent tumor to an aggressive variant that is associated with high mortality rate.

The aim of our study was to evaluate predictor factors for survival of patients with metastatic MTD(M1)

Methods: A retrospective study analysis of all patients with medullary carcinoma who were treated at Gustave Roussy Cancer Campus, Villejuif, France, between 1973-2014.

We studied the records of 500 patients, 96 of them had metastatic MTC. The analysis included demographics, sign and symptoms, pathological and biochemical parameters, and TKI treatment (number and periods) and outcome.

Results: 96 patients included in the analysis, mean age 48.4years, M:F 66:30. Mean tumor size at diagnosis-34.7mm. The mean time for DM from initial diagnosis was 57months. Mean Calcitonin, CEA and Chromogranin level at time of diagnosis of DM were 19478pg/ml, 905ng/ml and 1093ng/ml. Mean Calcitonin doubling time was 5.4. At the end of the study, 38 patients were alive (40%), whereas 58(60%) patients died. Diarrhea and pain were the most significant symptoms related to death (p=0.0011 and P-0.0048). Five year overall survival from appearance of DM was 46%.

Cox Proportional Hazard Model for overall survival reveal that TKI treatment period, Calcitonin doubling time, bone metastasis, mediastinal and abdominal lymph node metastasis and size of primary tumor were significant predictors of overall survival(p0.0001).

Conclusions: Patients with DM of MTC to the bone, mediastinal and abdominal lymph nodes and symptomatic patients had the worst prognosis. The preliminary results suggest that TKI treatment improve prognosis.

Poster Presentation (Sunday, April 7, 2019 10:20)

Percutaneous Ethanol Injection Treatment for Thyroid Cysts

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Introduction: Thyroid cysts although mostly benign, 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- Five consecutive patients (43.2±26.5 years; 100 % women) with symptomatic benign thyroid cysts which had relapsed after drainage, who underwent PEIT and completed at least 6 months of follow-up were studied. PEIT was conducted using the established procedure. Cyst diameter and volume at baseline and follow-up, and the volume of fluid removed were measured. Early and late complications were recorded.

Results: 5 patients underwent single session PEIT. Mean initial cyst volume was 38.6±46.2 ml with maximum diameter of 4.86±1.5 cm and mean extracted liquid volume 26.8±33.5 ml. During the procedure all patients experienced mild pain, three experienced moderate pain and flu-like symptoms in the first 72hrs and one also had fever of 38.8. No severe complications were observed. After 44±14 weeks of follow-up, cyst volume was reduced by 84.5±6.7% 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.

Poster Presentation (Sunday, April 7, 2019 10:20)

Subclinical Hypothyroidism and All-Cause Mortality among ST Segment Elevation Myocardial Infarction Patients Undergoing Percutaneous Coronary Intervention

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Introduction: Subclinical hypothyroidism (SCH) is defined as an elevated serum thyroid-stimulating hormone (TSH) level with a normal serum-free thyroxine level (FT4). The aim of this study was to investigate the association between SCH and short- and long-term all-cause mortality in a large cohort of patients with ST elevation myocardial infarction (STEMI).

Methods: We evaluated TSH and FT4 levels of 1593 STEMI patients without a known history of hypothyroidism or thyroid replacement treatment who were admitted to the coronary care unit and underwent primary percutaneous coronary intervention (PCI) between January 2008 and August 2017. The presence of SCH was defined as TSH levels ≥5 mU/ml in the presence of normal free T4 levels. Patients were assessed for short- (30 days) and long- term (1 year) outcomes.

Results: SCH was detected in 68/1593 (4.2%) STEMI patients. Patients with SCH had lower left ventricular ejection fraction (47% vs. 44% for those without SCH, p=0.014), older age (60 years), and family history of CAD, and were associated independently with 30-day mortality (HR 3.24, 95% CI: 1.22-8.63, p=0.02). Long-term mortality was significantly higher among those with SCH (16/68, 24%) than those without SCH (202/1525, 13%; p0.001). SCH was independently associated with long-term mortality following STEMI (HR 2.17, 95% CI:1.24-3.79, p=0.007, multivariable Cox regression model).

Conclusions: SCH is not uncommon among STEMI patients who undergo PCI and may serve as a significant predictor for higher short- and long-term mortality.

Familial Non-medullary Thyroid Carcinoma Has Similar Presentation and Disease Outcome than Sporadic Non-medullary Thyroid Carcinoma

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Background: The aggressiveness of familial non-medullary thyroid cancer (FNMTC) is controversial. We aim to study the short- and long-term outcomes of FNMTC patients treated at our institution. **Methods:** From a total of 518 papillary thyroid cancer (PTC) patients, 44 had 2 or more (8/44) affected family members. Clinical features, management and disease outcome were compared with 305 sporadic patients (SNMTC). **Results**: In FNMTC patients mean age was 45.9, 72.7% females, 95.5% PTC, 31% microcarcinoma, 42.5% multifocal, 5.1% ETE (TNM 8th), 3.1% N1, 5% M1 (2/40), 97.5% stage I-II TNM 8th edition (80% edition 7th) and 66.6% low ATA recurrence-risk; with no significant differences between groups. Both groups underwent similar surgical and radioiodine primary treatments. However, total thyroidectomy was performed in 97.6% FNMTC vs 86.9% SNMTC patients (p=0.07). Additional treatment during follow-up included repeated RAI in 27% and reoperation in 7.9% of FNMTC patients vs. 20% and 6.4% of SNMTC patients, respectively (p=ns). Persistent disease at 1 year was seen in 29.7% FNMTC vs 17.2% SNMTC (p=0.11) and at last visit in 7.1% (FNMTC) vs 10.7% SNMTC (p=0.66). Overall mortality was recorded in 4.2% (12/285) SNMTC patients vs 0% (0/41) FNMTC patients (p=ns). Median follow-up was borderline longer for the SNMTC (9 yr, range 1-53) compared to FNMTC (6 yr, range 1-32) group, (p=0.08). **Conclusions:** No significant differences were found in disease severity at presentation, treatment modality and disease outcome when comparing FNMTC to sporadic cases. Our results suggest that familial disease does not justify a more aggressive treatment.

Poster Presentation (Sunday, April 7, 2019 10:20)

Presentation of Thyrotoxicosis in Hospitalized Elderly Patients

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Introduction:

Thyrotoxicosis in the elderly may present differently than in younger indeviduals, and with the aging of the worlds` population it is imperative to obtain data in this age group.

Aim:

Our aim was to identify and characterize clinical and biochemical parameters of thyrotoxicosis in the elderly and to compare them to those of younger patients.

Methods:

We retrospectively evaluated files of patients older than 40 who were admitted to Rabin Medical Center in the years 2000-2018, and had suppressed TSH levels and increased thyroid hormone levels at admission. Clinical characteristics were compared between those older and younger than 70 years.

Results:

After exclusion of 42 patients (7 had non thyroidal illness, and 35 for multiple admissions) our cohort included 277 patients of which 157 were older than 70 (57%, mean 81.2±6.1) with a female predominance. TSH levels, thyroid hormone levels and heart rate at admission were comparable between the groups. Etiology was more likely to be Graves` disease or thyroiditis among those younger than 70 years, and toxic adenoma/toxic multinodular goiter or amiodarone induced thyrotoxicosis in those older than 70 years . Weight loss, fatigue, apathy, new and chronic fibrillation and goiter were all significantly more common in the elderly. Similar results were obtained when we excluded those who were treated with thyroxine before hospitalization.

Conclusions:

Hospitalized elderly individuals with thyrotoxicosis more commonly present with non-classical symptoms and atrial fibrillation, compared to younger patients. Low threshold for evaluation might be appropriate in this age group.

Poster Presentation (Sunday, April 7, 2019 10:20)

Adherence to Active Surveillance and Clinical Outcomes in Patients with Indeterminate Thyroid Nodules Who Are Not Referred for Thyroidectomy

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Introduction: Outcomes of patients with cytologically indeterminate thyroid nodules who are not initially referred for thyroidectomy have hardly been investigated. One study of patients with gene expression classifier (Afirma) benign Bethesda 3(B3) nodules noted similar rates of ultrasound (60.2%) and thyroidectomy (11.4%) during 20 months' follow-up to patients with benign cytology. We previously reported findings in patients after thyroidectomy for B3/B4 nodules. The present study sought to investigate follow-up adherence and outcomes of unoperated patients with B3/B4 nodules.

Methods: File review of consecutive patients attending a tertiary hospital diagnosed with B3/B4 thyroid nodules by FNA in 2011-2012 and followed without initial thyroidectomy.

Results: There were 157 patients with B3 nodules and 15 with B4; median follow-up was 5 years. Ultrasound was repeated in 122/157 B3 patients (77.7%), demonstrating nodular growth in 22 (18%). FNA was repeated in 73/157 B3 patients (46.5%), and reported as B2 in 54 (75%) and B3 in 12 (16.4%). Thyroidectomy was eventually performed in 11 B3 patients (7%) and 5 B4 patients (33%). Thyroid cancer was diagnosed in 4 patients and 3 patients, respectively. Of the 10 unoperated B4 patients, one had thyroid lymphoma and 3 died of unrelated causes soon after FNA; in 2, older age precluded surgery.

Conclusions: Most patients adhere, at least partially, to follow-up schedules. When surgery is not performed for B4 thyroid nodules, a clear reason is usually evident. For B3 nodules, rates of neck ultrasound and eventual thyroidectomy during surveillance are similar to those for benign or Afirma-negative thyroid nodules.

Poster Presentation (Sunday, April 7, 2019 10:20)

Surveillance of Patients with Differentiated Thyroid Cancer: The Impact of Stimulated Thyroglobulin Measurement with or without Whole-body Scan

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Objective: Surveillance of patients with Differentiated thyroid cancer (DTC) includes measurements of stimulated Thyroglobulin (sTg), low dose whole-body scan (WBS), or a combination of the two. Although sTg testing is widely recommended, the necessity of WBS is debated. According to 2015 ATA guidelines, WBS is indicated only in intermediate or high-risk patients. This study evaluated characteristics and outcomes of patients who routinely underwent combined WBS and sTg testing.

Methods: Data of DTC patients followed-up in a single medical center between 2008 and 2018 was retrospectively analyzed. sTg levels above 10 ng/mL were considered positive. Outcomes included disease persistence or recurrence and need for additional treatment.

Results: Of 643 DTC patients, 272 met inclusion criteria (mean age 46.5±15.2, 79% female). Mean duration of follow-up after stimulation was 11.6±6.8 years. Of these patients, 191 (70%) were sTg(-) and WBS(-); 48 (17.6%) were sTg(-) and WBS(+); and 33 (12%) were sTg(+)with either WBS(+) or (-). There was no difference in baseline demographic, clinical or pathological characteristics between sub-groups. Of the entire cohort, 39 patients had evidence of structural recurrence during follow-up. Eighty patients received additional treatment. Logistic regression analysis, adjusted for number of ablations prior to WBS, risk stratification, initial treatment response and sTg status, revealed that WBS(+) is independently associated with disease recurrence (P=0.011), and necessity of further treatment (P0.001).

Conclusion: In our study, WBS(+) and sTg(-) status was noted in a significant proportion of patients, and associated with disease outcome. WBS may thus deserve a role in routine surveillance of DTC patients.

Poster Presentation (Sunday, April 7, 2019 10:20)

Thyroid Function Dynamics in Cancer Patients Treated with Immunotherapy

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Background: Thyroid dysfunction following treatment with immune checkpoint inhibitors (ICIs) is a prevalent adverse effect.

Aim: To assess the incidence and patterns of thyroid dysfunction in cancer patients treated with ICIs.

Methods: A retrospective study, based on a tertiary hospital endocrine oncology specializing unit experience. Data on thyroid function tests of cancer patients treated with ICIs including Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab and Durvalumab during the years 2015-2018 were retrieved from the clinical database of Chaim Sheba Medical Center.

Results: A total of 1763 cancer patients received the relevant ICIs between January 2015 and October 2018, with 35,137 thyroid function tests recorded (11,046 FT3, 11,164 FT4 and 12,927 TSH measurements). One hundred and two patients had at least 3 FT4 measurements two weeks before ICIs initiation or later. The classic thyroid function pattern described in acute thyroiditis was the most prevalent. The dominant pattern is an early rapid elevation of FT4 with relatively negligible FT3 change, followed by a rapid decline in FT4 (n=57). Among the patients with FT4 decline, eight had documented second phase hypothyroidism. The rate of hypothyroidism is probably underestimated due to timely thyroid hormone replacement. Two hundred and thirty six patients had abnormal function test(s), including 227 with hyperthyroidism, 52 with hypothyroidism, 21 patients with both documented.

Conclusion: Thyroid dysfunction is a prevalent adverse effect of immunotherapy, occurring relatively early after treatment initiation. The rate of thyroid dysfunction detected in our cohort is lower than the rate reported in the literature.

Poster Presentation (Sunday, April 7, 2019 10:20)

A Curious Case of Thyrotoxicosis

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Thyrotoxicosis may present in unusual ways, delaying the diagnosis.

Aim: To present a case of thyrotoxicosis that was initially missed because of a very unique presentation.

Methods: Case report. A 52 year old woman was admitted with new complaints of weakness, anorexia and 3kg weight loss. On examination she was afebrile, BP 120/76, sinus tachycardia 160/minute, weak, pale and jaundiced. Investigations: Hemoglobin 6.8g/dl, MCV 98, total bilirubin 12.83, direct 6.69, ALP 167, AST 131, ALT 100, GGT 216, amylase 87. Abdominal CT showed a normal biliary tree but hypodense areas up to 16 mm in the pancreas. The following day her amylase rose to a peak of 2703 returning to normal over three days. Total bilirubin rose to a peak of 31. Direct 17.26. AST, ALT, ALP and GGT rose to twice normal. An abdominal MRI revealed changes consistent with pancreatitis, possibly of autoimmune origin. She was treated conservatively and was discharged for outpatient follow-up. The following week she was readmitted because of weakness and persistent tachycardia. The total bilirubin was 5.36, direct 2.68, LFTs unchanged. Incidental thyroid function studies revealed a TSH of 0, FT4 44pM, FT3 21pM. The diagnosis of Graves disease was made.

Results: With administration of mercaptizole, thyroid function, bilirubin , LFT and hemoglobin returned to normal.

Conclusions: We describe a case of thyrotoxicosis presenting with anemia, jaundice and pancreatitis obscuring the diagnosis of Graves disease. The cause of the pancreatitis is unclear. Possibilities include hypercalcemia, autoimmune or other hitherto undescribed mechanism.

Poster Presentation (Sunday, April 7, 2019 10:20)

Fine Needle "Parathyroidectomy"

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Background: Spontaneous or fine-needle aspiration (FNA)-induced remission of primary hyperparathyroidism (PHPT) has been reported, especially for cystic lesions. However, the disease generally relapses over a short time. There are few reports of long term remission after aspiration of solid parathyroid adenoma.

Case report: A 60-year-old men with type 2 diabetes mellitus and paroxysmal atrial fibrillation treated with novel anticoagulants had hypercalcemia from PHPT. Sestamibi parathyroid scintigraphy showed nonhomogenous uptake in the thyroid left lobe without focal lesion. Ultrasound revealed a large hypoechoic oval lesion posterior to the left lobe with maximal diameter of 40mm suggestive of parathyroid adenoma. The patient was referred for FNA with needle washout for PTH. This confirmed the diagnosis of left parathyroid adenoma. At follow-up the patient reported suffering neck pain for one week following the FNA. Biochemical evaluation revealed normalization of the hypercalcemia. Ultrasonography revealed significant shrinkage (90%) of the adenoma. 18 months after the FNA the patient is still normocalcemic with only mildly elevated PTH and without enlargement of the parathyroid lesion.

We postulate that US-FNA-induced intracapsular hemorrhage followed by shrinkage of the parathyroid adenoma may explain the partial hormonal and anatomical remission of PHPT. However, in the absence of histological or sonographic verification, this remains only a hypothesis, with the role of the FNA unproven.

Summary: We present a case of PHPT due to an enlarged hyperfunctioning parathyroid that underwent long-term (18 months) clinical and ultrasonographic partial remission following ultrasound assisted FNA that might be a consequence of intracapsular hemorrhage.

Poster Presentation (Sunday, April 7, 2019 10:20)

Amiodarone-induced Thyrotoxicosis: A Late, Prolonged and Serious Complication

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Background: Amiodarone treatment is often associated with thyroid dysfunction. Amiodarone`s high iodine content can act directly on the thyroid and induce increased synthesis of thyroid hormones or lead to a destructive thyroiditis. Frequently, these mechanisms overlap and treatment can be challenging.

Aim: To describe clinical and laboratory characteristics of patients who develop clinically significant AIT.

Methods: Data from consecutive cases of AIT seen at local endocrine clinics beginning in January 2018 until present were collected from computerized patient`s files in the relevant HMO database.

Results: We describe seven patients (five male), mean age 68 years (range 40 - 84), who developed AIT, with six of them requiring hospitalization. Mean maximal FT4 was 97 pmol/L, (range 36 -154 pmol/L). None had goiter or prior thyroidal illness and only one had positive anti-TPO. The mean duration of treatment prior to AIT diagnosis was 33 months (range 24-45). Mean time from last thyroid function test to AIT diagnosis was 11.3 months (range 6-24). Six of the patients received a combination of high dose methimazole, prednisone and cholestyramine. At 20 weeks of follow-up, only two of the patients regained euthyroidism, whilst treatment for the others is still ongoing.

Conclusions: Our data demonstrate that AIT is a severe illness that can develop late in the course of treatment. Most cases are challenging to treat and necessitate multiple medications. This implies that more frequent and prolonged monitoring of thyroid function tests is required in patients treated with amiodarone.

Poster Presentation (Sunday, April 7, 2019 10:20)

Igfbp1 as a Repression Target of PGC-1α in the Context of Blood Glucose Homeostasis

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Maintaining blood glucose levels within a narrow range is a crucial physiological function dependent on numerous metabolic pathways. PGC-1α is a pivotal metabolic transcriptional coactivator that associates with HNF4a and Foxo1 in liver to activate the expression of gluconeogenic genes, thus controlling blood glucose levels. Our studies revealed, surprisingly, that PGC-1α is involved in transcriptional repression. As part of our attempts to identify major targets for PGC-1α repression activity in liver-derived cell lines, we identified IGFBP1 as one such target using microarray analysis. IGFBP1 is a regulator of insulin sensitivity and blood glucose, and has been previously demonstrated to improve glucose tolerance and insulin sensitivity when overexpressed. Our microarray results were further validated by qPCR in HepG2 and FaO cells. Using mice with a liver-specific deletion of PGC-1α we show that PGC-1α specifically represses IGFBP1 in mouse liver, but does not significantly regulate the levels of other IGFBP family members. To further implicate PGC-1α in direct repression of the IGFBP1 gene, chromatin immunoprecipitation studies were performed in HepG2 indicating PGC-1α is associated with the IGFBP1 promoter in cultured cells. Additionally, as HNF4α has been shown to down-regulate the expression of IGFBP1, and PGC-1α is a known binding partner of HNF4α, we generated cells null for HNF4α using CRISPR-Cas9 technology for future studies of HNF4α involvement in PGC-1α mediated repression of IGFBP1. Collectively, our studies point to IGFBP1 as a potentially important target gene for PGC-1α repression in liver, with possible implications for our understanding of mechanisms controlling blood glucose homeostasis.