האגודה הישראלית לאנדוקרינולוגיה IES Israel Endocrine Society

The 46th Annual Meeting of the Israel Endocrine Society

20-21, March, 2017
Kfar Maccabiah Hotel, Ramat -Gan

Program & Abstract Book

WELCOME ADDRESS

Dear members, colleagues, and friends,

On behalf of the new executive committee of the Israel Endocrine Society, it is our pleasure to welcome you to our 46th annual meeting. After convening for two successive years outside of Tel Aviv (Ashkelon and Jerusalem), we are back in the Tel Aviv area.
This is the first scientific meeting that our new organizing team put together, and we are hopeful it will live to everybody's expectations.

As part of our ongoing efforts to strengthen our ties with the European Society of Endocrinology and its affiliate societies, we will be hosting our first ESE lecture that will be delivered by Renato Pasquali from Italy. This year we are honored by the participation of several guest speakers who came from afar to be with us.

We are indebted to John Nestler, Renato Pasquali, Jan-Wilhelm Kornfeld, and Yaron Tomer, who will be taking part in plenary lectures, symposia, and meet-the professor sessions. We are no less thankful to our many local invited speakers, Sandra Alboim , Gad Asher, Izhar Ben Shlomo, Yuval Dor, Elena Dumin, Tal Imbar, Shalev Itskovitz, Yehonatan Saharabi, Ram Weiss, and Leonid Zeitlin, who didn't travel far but put in the time and effort to contribute to a varied and exciting scientific program.

We received an unprecedented number of abstracts, and in addition to slightly enlarged oral presentations sessions, you should be ready for a very intense poster session.

This year, we will feature a "Year in" session that will allow us to get the highlights of notable advances in the fields of adrenal, pituitary and reproduction.
On March 20th, the Israel Endocrine Society will honor Prof. Ytzik Koch, one of the founders and pillars of our society for his long term unconditional contribution and commitment. Please join us for this informal gathering that will take place in the afternoon, just before the MTP sessions.

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 certain that out joint efforts together with you attendance will make this meeting a remarkable one.

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

Looking forward to seeing you soon in Kfar HaMaccabiah.

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

IES EXECUTIVE COMMITTEE

Avraham Karasik, M.D., President
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Karen Tordjman, M.D

תודתנו נתונה לחברות נותנות החסות והמציגים על תמיכתן הנדיבה:

פרופ' הנס יוחנן לינדנר ז"ל – מילים לזכרו

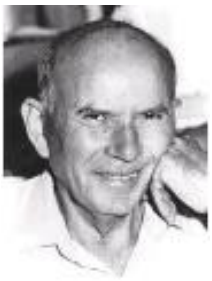
פרופ' הנס יוחנן לינדנר נולד בשנת 1922 בגרמניה ועלה ארצה עם הוריו בשנת 1936. לאחר מלחמת השחרור הוא למד רפואה וטרינארית בסידני (אוסטרליה) וסיים בהצטיינות. את לימודיו לתואר Ph.D. הוא השלים באוניברסיטת קיימבריג' שבאנגליה. עם תום לימודיו, חזר לינדנר לאוסטרליה, התמנה כחוקר בכיר ב- Commonwealth Scientific Research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

2017- ד"ר סימונה גלסברג

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- ד"ר עמית עקירוב

Program at a Glance

<table>
<tr><th colspan="3">Monday, March 20, 2017</th></tr>
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<tr><td>08:30-10:00</td><td colspan="2">Oral Presentations: 3 parallel sessions
Reproduction
Diabetes (Basic)
Bone</td></tr>
<tr><td>10:00-10:15</td><td colspan="2">Coffee Break</td></tr>
<tr><td>10:15-10:30</td><td colspan="2">Opening Session</td></tr>
<tr><td>10:30-11:20</td><td colspan="2">Plenary lecture 1: <u>John E Nestler</u> , Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA USA
Chair- Yossi Orly
“Polycystic Ovary Syndrome and Risks for Diabetes and Cardiovascular Disease: Therapeutic Implications”</td></tr>
<tr><td rowspan="5">11:20-12:50
Parallel Symposia</td><td>The ESE lecture
Chair: Daniela Jakubowicz</td><td>Symposium 2: Obesity and Metabolism
Chairs: Eddy Karnielli; Amir Tirosh</td></tr>
<tr><td><u>Renato Pasquali</u> - Laboratory Definition of Hyperandrogenism, and its Pathogenesis.

University Alma Mater Studiorum of Bologna, Italy.</td><td><u>Gad Asher</u> –
Circadian Clock Control of Metabolism

Department of Biomolecular Sciences, Weizmann Institute of Science</td></tr>
<tr><td>Symposium 1: PCOS
Chairs: Karen Tordjman; Daniela Jakubowicz</td><td><u>Ram Weiss</u> –
The Impact of Bariatric Surgery on Beta cell Function
Hadassah Medical Center, Hebrew University, Jerusalem</td></tr>
<tr><td><u>Izhar Ben-Shlomo</u>- The Impact of Carbohydrate-Poor Diet on Gut Microbiome of Women with PCOS.

Baruch Padeh Medical Center, Poriya & Faculty of Medicine in the Galilee, Bar Ilan University</td><td><u>Gabriella Liberman Segal</u> –
Role of Gut Hormone in Obesity Therapy

Institute of Endocrinology; Sheba Medical Center</td></tr>
<tr><td><u>Rina Meidan</u> -Distinct Hypoxic Responses in PCOS-Derived Granulosa Cell
The Hebrew University</td><td><u>Talia Diker-Cohen</u>- Leptin and Lipodystrophy.

Institute of Endocrinology and Metabolism Rabin Medical Center, Campus Beilinson</td></tr>
</table>

12:50-13:50	**Lunch Break**	
13:50-14:40	**Plenary lecture 2:** **Jan-Wilhelm Kornfeld** ,Max Planck Institute for Metabolism Research, D-50931 Cologne, Germany. Chair- Galia Gat-Yablonski "DeCoding Obesity - Control of Metabolism by the Noncoding Genome "	
	Parallel Symposia	
14:40-16:10	**Symposium 3:** **Transitional Endocrinology** **"Tips from the pediatric to the adult endocrinologist"** Chairs: Naomi Weintrob; Nehama Zuckerman-Levin	**Symposium 4:** **Current topics in the Endocrine Labs - What Clinicians should know** Chairs: Naftali Stern; Yulia Schneider
	Yardena Tenenbaum- Combined Pituitary Hormone Deficiency (CPHD): Significant Issues from Infancy to Adulthood *Head, Pediatric Endocrine Unit; Ha'Emek Medical Center, Afula*	**Yehonatan Sharabi** -Diagnosis and Evaluation of the Hypertensive Patient and the Use of Aldosterone/Direct renin Concentration Ratio *Hypertension Unit, Sheba Medical Center*
	Leonid Zeitlin - Osteoporosis and related diseases in children *Department of Pediatrics; Dana-Duek Children's Hospital*	**Elena Dumin** - Mass spectrometry-Based Metabolomics: Application to Adrenal Diseases *Clinical Biochemistry Laboratory Rambam Medical Center*
	Mariana Rachmiel -Disorders of Gonadal Differentiation *Head, Pediatric Endocrine Unit; Assaf Harofeh Medical Center*	**Sandra Alboim** -National Project to Determine 11-Deoxycortisol Reference Range in the Israeli Population *Central Laboratory Maccabi Healthcare Services*
		Hannah Kanety - Biotin Treatment Cause Misleading Hormones Results *Institute of Endocrinology , Sheba Medical Center*
16:10-16:40	**Ceremony in Honor of Prof. Y. Koch**	
16:30 - 17:30	MTP 1 -PCOS **John E Nestler** and **Renato Pasquali** PCOS-Tips for the Endocrinologist	**MTP 2** –**Yaron Tomer**- Autoimmune Thyroid Diseases in Pregnancy

Tuesday, March 21, 2017		
07:30-08:15	**Registration and Gathering**	
08:15-10:00	**Oral Presentations: 3 parallel sessions** Diabetes and Metabolism (clinical) Thyroid Hormones & Cancer	
10:00-10:15	**Coffee Break**	
10:15-11:00	Posters	
11:00-12:30	**General Assembly and Prizes session** **Chair** –Avraham Karasik **Lindner Prize Lecture** (25 min) **Chowers Prize Lecture** (15 min) **Prizes for Best Clinical/Basic Abstracts** (10 min) **IES Members Assembly Meeting** VAAD report (20 min) Accountant Report (10 min)	
12:30-13:30	**Lunch Break**	
13:30-14:20	**Plenary lecture 3:** **Yaron Tomer,** Chair, Department of Medicine, Albert Einstein College of Medicine Chair: Carlos Benbassat **"**Autoimmune thyroid diseases: from gene mapping to novel drug targets"	
14:20-15:50	**Parallel Symposia**	
	Symposium 5: The Year in Endocrinology Chairs: Ben Glaser, Yona Greenman	**Symposium 6: Cellular Heterogeneity** Chairs: Yehiel Zick; Gil Leibowitz
	Tal Imbar - The year in reproduction**.** *IVF Unit, Human Placenta Research Center; Dept. of Obstetrics & Gynecology; Hadassah-Hebrew University Medical Center*	**Assaf Rudich** - Heterogeneity of adipose tissues and cells - a basis for subphenotyping obesity. *Department of Clinical Biochemistry. Faculty of Health Sciences, Ben Gurion University*
	Ilan Shimon - The year in pituitary. *Institute of Endocrinology and Metabolism Rabin Medical Center, Campus Beilinson*	**Shalev Itskovitz** - Cellular heterogeneity in the liver: from single RNA molecule organization to organ function. *Department of Molecular Cell Biology, Weizmann Institute of Science*
	Merav Fraenkel - The year in adrenal. *Endocrine Unit Soroka Medical Center*	**Yuval Dor**- Plasticity of the endocrine pancreas in diabetes. *Department of Developmental Biology and Cancer Research; The Hebrew University-Hadassah Med School*
15:50-16:05	**Coffee Break**	

16:05 -17:30	**MTP1**	**MTP2**
Parallel MTP	**Zeev Hochberg** Short stature. Does changing height matter?	**Pnina Rotman and Iris Vered** Fragile and challenging cases in the bone metabolism clinic

Abstracts

Application of FRAX-based Osteoporosis intervention: impact on public health using real-world data

Inbal Goldshtein[1,2], Moshe Leshno[1]
[1]Tel Aviv University, Faculty of management
[2]Maccabi Healthcare Services, Research Institute

Objective: The WHO fracture risk calculator has been recently calibrated to Israel, yet there is no universal agreement on a specific intervention threshold. We aimed to assess the precision and implications of the most common FRAX-based intervention heuristics: NOF (National Osteoporosis Foundation) and NOGG (National Osteoporosis Guideline Group) guidelines, as well as the WHO diagnostic criteria by bone mineral density (BMD).

Methods: FRAX scores were retrospectively calculated for all 50-90 years old female members of Maccabi healthcare services at the year 2004. The proportions recommended for anti-osteoporosis therapy were calculated according to NOF, NOGG and the WHO diagnostic criteria. Their detection rates were assessed by comparison to incident major osteoporotic fractures (MOF) observed during the following 10 years.

Results: Among 141,320 women (median age=58) a total of 13.5% and 2.9% MOF and hip fractures events were observed within 10 years. Overall, 17.3% and 2.8% of the population would have been indicated for therapy by NOF and NOGG respectively. The number needed to treat to prevent one MOF/hip fracture was similar (3.7/9.3 with NOF, 3.8/8.7 with NOGG), yet the observed balanced accuracy was higher with NOF: 74.1% vs. 54.2% for hip fractures. Among the sub-population of patients with available baseline BMD data (n=16,578): NOF, NOGG, osteoporotic femur neck (FN) T-score and osteoporotic T-score (spine/FN) criteria were met by 30.5%, 9.3%, 9.0% and 24.6% of the population, with balanced accuracy of 70.1%, 56.5%, 62.3% , 62.3% respectively for hip fractures detection.

Conclusions: In this large, population-based study, the NOF fixed threshold exhibited higher overall accuracy as compared with the age-varying NOGG approach and the WHO BMD-based diagnostic criteria. NOF would expand the indication for therapy by 24% as compared with the current mainstay practice of bone-density-only based decision, whereas NOGG would decrease it by 62%.

Fragility fractures in patients admitted to Assaf Harofeh Medical Center: Clinical characteristics and pre-fracture risk assessment.

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Introduction: Timely diagnosis and optimal treatment of osteoporosis prevents fractures. However, the majority of people presenting with a fragility fracture are neither assessed for osteoporosis nor appropriately managed.

Aims: To investigate the pre admission screening process and pre fracture risk assessed by FRAX with no BMD data, aiming to improve primary prevention.

Methods: A retrospective analysis of prospective data collection of new fragility fracture cases admitted to the orthopedic ward at Assaf Harofeh Medical Center from March to December 2016.

Results: We enrolled 103 patients, 81.6% female, mean age 78.4 yr , mean BMI 26. Comorbidities included: diabetes 35%, steroids use 7.8%, and active smokers 9.7%. History of previous fracture was recorded in 33% patients. Fracture location was hip 74.8%, spine 13.6%, humerus 3.9%, tibia 2.9%, radius and ribs 1% each. In 78% the fracture occured in-doors. Treatment at admission included surgery in 76.2% (89.6% for hip, 14.3% for spine).

Only 35 patients (34%) had a previous diagnosis of OP, 26 of them were treated at any point, only 17 were treated at admission. Comparison of naïve vs known OP groups revealed that males are less likely to have OP diagnosis while fracture site did not differ between groups.

Excluding OP active treated patients (n=86), the pre-fracture risk in males and females was 7.6 and 9.5% for the hip (p=ns), with 82.4 and 80.9% of the male/female above the 3% cut off. The major osteoporotic pre-fracture risk in males and females was 12 and 19% (p0.01), with 12 and 50% above the 20% cut off.

Conclusion: Patients presenting with fragility fracture have a pre fracture risk high enough to be used to tag them for thorough OP evaluation and possible treatment. Our small cohort supports a wider use of no-BMD FRAX score system as a tool for primary prevention.

Atypical Femoral fractures among patients from the Soroka Fracture Liaison Service

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Background

Osteoporotic hip fractures are growing medical and financial burden. Sub-trochanteric fractures represent up to 10% of hip and femoral fractures. Of those only a subset can be defined as atypical femoral fractures (AFF) using the criteria developed by the task force of the American society for bone and mineral research (ASBMR). It was our aim to characterize AFF among our cohort of patients participating in the Soroka University Medical Center (SUMC) Fracture Liaison Service (FSL).

Methods

As of July 2014, patients over age 50 admitted with hip fracture were offered investigation, and treatment by the FLS. All sub-trochanteric fractures were evaluated by an expert radiologist. Of those, AFF were defined using the ASBMRs` criteria. Demographic data, lab assessment and type of anti-osteoporotic medications of patients with AFF were collected.

Results

As of October 2016, 917 patients were admitted with hip fracture, of whom 608 joined the project; mean age was 79 years, 70% were females. Fifty one (8.3%) had sub-trochanteric fracture. Their radiology films were reviewed by a radiologist and 11 (1.8%) were judged to fulfill the ASBMR task force criteria for an AFF. The mean age of patients with AFF was 79.55±10.36, 73% were female. Sixty four percent (7/11) were not exposed to bisphosphonates before the AFF occurred. Among 4/11 patients who were treated with bisphosphonates prior to the AFF, the median exposure time was 23 months. There were no clinically relevant differences between the AFF group and the rest of the cohort of patients with typical osteoporotic hip fracture, including exposure to bisphosphonates.

Conclusions

In our cohort of patients with osteoporotic hip fractures treated by the FLS in SUMC, 1.8% presented with AFF. There were no clinically significant differences concerning demographic, laboratory, and history of bisphosphonate exposure between patients with AFF and the rest of the cohort.

Long-Term Follow-Up of 10 Patients with Pseudohypoparathyroidism (PHP)

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Background: Pseudohypoparathyroidism (PHP) is a group of rare heterogeneous genetic disorders characterized by resistance to the action of different hormones that activate the stimulatory G protein (Gs) – coupled pathway. The two main subtypes, PHP type Ia and Ib, differ mainly by the presence of a typical phenotypic trait defined as Albright`s hereditary osteodystrophy in PHP type Ia. Both subtypes are caused by molecular alterations in the *GNAS* gene encoding the -α subunit of Gs protein.

Objective: To describe the clinical, biochemical and molecular characteristics of 10 patients with PHP (5 with Ia, 5 with Ib; 9F, 1M) and to evaluate them in long-term follow-up.

Results: All patients were of unrelated families. The follow-up period was as long as 18 years. Patients with type Ia were referred due to short stature or abnormal thyroid function; patients with type Ib were referred because of hypocalcemia. TSH resistance was the first hormone resistance detected in all patients with type Ia and in 2 patients with type Ib. All patients with type Ia were normocalcemic at referral but PTH levels increased with time, ranging from 9 months to 4 years after referral. Hypocalcemia was found in 3 of these patients within 5.5 to 11.5 years after PTH increase. Short final height was shown in 4 patients with type Ia, 3 of these having GH deficiency. 3 patients with type Ib were short and partial GH deficiency was diagnosed in one of them. All patients with type Ia had elevated gonadotropins but spontaneous pubertal onset was shown, albeit with late menarche and secondary amenorrhea. Pubertal growth spurt was absent in all girls and final height was compromised. Molecular analysis revealed, a novel deletion spanning exon 7 to 13 in patients 3 and 4, a novel missense mutation in exon 5 (c.320TC) in patient 5; and a known missense mutation in exon number 9 in patients 1 and 2 (c.692 CT, p.R231C). All patients with type Ib had broad methylation defects consistent with a sporadic form of PHP-Ib.

Conclusions: The phenotypic features of PHP are variable; therefore, primary physicians` awareness of these disorders is warranted. Hormonal resistance may develop over time, and long-term follow-up is thus indicated. Molecular analysis is important for confirming the diagnosis, and for genetic counseling.

Preliminary experience with trabecular bone score (TBS) assessment in Israel

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Bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry (DXA) is pivotal for the diagnosis of osteoporosis and for monitoring treatment efficacy but has several limitations. It is a two dimensional imaging for a three dimensional structure, influenced by several artifacts and measures mineral content of the tissue instead of its microarchitecture. Recently, a software analyzing DXA images and evaluating vertebral bone microstructure (TBS) became available. Strong correlation exists between TBS and fracture risk, both independent of the BMD and synergistic with it, and TBS has been imbedded into FRAX risk calculation.

The objective was to describe our preliminary experience with TBS, to evaluate the added value of TBS measurement and to identify the population who benefits most from the addition of TBS to DXA measurements.

Methods: DXA scans of consecutive patients undergoing routine BMD measurements were analysed. TBS was derived using Medimaps software pilot version. The patients completed a questionnaire regarding risk factors relevant to the FRAX. The FRAX scores for hip and major osteoporotic fractures (MOF) were calculated with and without TBS.

Results: 208 patients (27% men) were included (mean age 66$\pm$11 years). Mean T-scores at spine and femoral neck were -1.17$\pm$1.6 and -1.5$\pm$0.9, respectively. Mean difference between FRAX and FRAX+TBS risk for hip fractures was 0.4$\pm$0.6 % (NS) and 1.0$\pm$1.1 % (NS) for MOF. Comparable FRAX and FRAX+TBS values were also recorded in a subgroup of patients with borderline FRAX scores. The largest difference (+25% for hip fracture and +17% for MOF) was noted in a young patient with IBD on glucocorticoid treatment at a very high fracture risk, even before adjusting for TBS.

Conclusions: In a convenience sample of BMD examinees, TBS had a low added value for fracture risk assessment. The sample size did not allow us to test the discriminatory potential of TBS in patients with secondary osteoporosis, a subgroup previously reported to benefit from TBS incorporation.

Alendronate Reduces the Risk of Bone Metastases in Osteoporotic Women with Early Breast Cancer

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Background: Bisphosphonates (BP) are widely used in osteoporosis treatment. By reducing the production of osteolysis-derived growth factors, BP may render the bone microenvironment unsupportive of tumor cell survival thereby reducing breast cancer recurrence. Recent data on the association between oral bisphosphonates and disease outcomes in patients with breast cancer are scarce, and there is no data available on Alendronate which is the most common oral agent for the treatment of post-menopausal osteoporosis.

Aim: To examine the association between previous oral bisphosphonate exposure and the incidence of bone metastases in osteoporotic women diagnosed with early breast cancer.

Subjects and methods: This historical cohort study was conducted at the oncologic clinic at Tel Aviv Souraski Medical Center. The study population included postmenopausal women with early breast cancer, diagnosed between January 1'st 2002 and December 31'st 2012. We reviewed medical files to collect data on cancer characteristics, diagnosis of osteoporosis, prior bisphosphonate exposure and outcome. The study protocol was approved by the local medical ethical committee.

Results: We reviewed 1000 consecutives files, 925 were identified as early breast cancer patients. Among them 297 patients were osteoporotic, 145 were treated with bisphosphonates before cancer diagnosis, and 81 were osteoporotic bisphosphonate naïve women, for the remaining 67 the exposure to bisphosphonates was not ascertained. Alendronate was the agent in 90% of the cases, and Risedronate in the remaining 10%. BP-treated women were older than the naïve ones (67.9 vs 64.6, $p=0.013$). No significant differences were noted regarding BMI, smoking status, parity or socioeconomic status. Cancer characteristics were similar between the two groups including tumor grade, positive lymph nodes and hormonal receptor status. The treatment received was similar except for naïve women receiving more aromatase inhibitors (49.5% vs 43.6%, $p=0.005$). A Cox proportional hazards survival model adjusted for age at diagnosis, BMI, smoking status, breast cancer family history, HRT use, and tumor grade showed that previous exposure to oral bisphosphonates significantly reduced the incidence of bone metastases: HR=0.009 CI (0.004-0.403) $p<0.002$.

Conclusions: Alendronate, the most common oral bisphosphonate prescribed for the treatment of osteoporosis, reduces the incidence of bone metastases in postmenopausal women with early breast cancer. Women at risk may benefit from early oral bisphosphonate treatment.

Connexin 43 mediated Gap Junction Intercellular Communication Promotes the Propagation of Hepatic ER Stress in Obesity

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Endoplasmic reticulum stress (ERS) is an important mechanism in the pathophysiology of obesity induced insulin resistance. The link between ERS and insulin resistance is well characterized at the cellular level. However, the role of cell-cell communication and the coordinated response at the tissue level is unclear. Increased gap junction (GJ)-intercellular communication, primarily composed of connexin (Cx)43, was shown to play a key role in the maladaptive tissue response to various stresses, and was implicated in the pathogenesis of atherosclerosis and neurodegenerative diseases, which similarly to obesity, are characterized by chronic low-grade inflammation and ERS. In this study we demonstrate that Cx43 is increased in various cell lines following ERS induction (in both gene expression and protein level). GJ mediated cell-cell coupling was also increased under these conditions. When ER stressed cells ('donors') were co-cultured with ERS-naïve ('recipient') cells, an inter-cellular transmission of ERS signals and activation of the unfolded protein response was demonstrated in intact cells ('bystander response'). This response resulted in chaperon consumption and impaired folding capacity of the recipient cells. Knock down of Cx43 prevented the transmission of ERS from 'stressed' cells to ERS naive cells. Diet induced obesity in mice resulted in hepatic ERS and in upregulation of Cx43 in the liver. In addition, co-culture of isolated hepatocytes from HFD mice with hepatocytes from lean mice resulted in transmission of ERS from obese hepatocytes to the intact hepatocytes in a Cx43-dependent manner. Taken together, our results suggest that in obesity, the increased Cx43-mediated cell-cell coupling may become maladaptive by allowing tissue propagation of ERS. This maladaptive response to over-nutrition may further aggravate liver ERS and worsen hepatic and systemic insulin resistance.

Endoplasmic Reticulum (ER) Stress Induces Diabetes By Impairing Postnatal β-cell Proliferation And Function

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Introduction- ER stress plays an important role in the pathophysiology of type 1 and type 2 diabetes (T1D and T2D); it is widely believed that in diabetes chronic ER stress induces apoptosis, resulting in decreased β-cell mass. *Akita* diabetes is a genetic form of ER stress-induced diabetes, due to proinsulin gene mutation causing misfolding. We studied the mechanisms of *Akita* diabetes.

Aim- Studying life-long changes in β-cell mass in *Akita* mice and the role of apoptosis, altered proliferation, or degranulation in β-cell dysfunction.

Methods- Pancreata were immunostained for islet hormones (insulin, somatostatin, glucagon), transcription factors (PDX-1, NKx6.1), proliferation markers (Ki67, PCNA, phosphohistone H3) and apoptosis (TUNEL). β-Cell differentiation determined by cre/loxP-based genetic lineage tracing.

Results- In diabetic *Akita* mice, β-cell mass was decreased ~70% compared to age-matched controls. Surprisingly, apoptosis was rare: few TUNEL+ β-cells were identified. β-Cell proliferation was 1%, similar to controls. Lineage tracing indicated 2% β-cells (YFP+) were degranulated or misexpressed somatostatin or glucagon without insulin. Thus, decreased β-cell mass in adult *Akita* mice was not due to β-cell dedifferentiation or changes in proliferation or apoptosis; we therefore studied postnatal β-cell dynamics. In controls, during first 3 weeks of life β-cell proliferation was ~10-fold higher than in adult animals, leading to 3-fold increased β-cell mass. In *Akita* mice, β-cell proliferation and Nk6.1 and PDX-1 expression was decreased by ~50%; β-cell mass at day 21 was 60% reduced. Insulin store was markedly depleted, insulin secretion attenuated, and glucose intolerance present. Treatment of newborn *Akita* mice with the chemical chaperone TUDCA for 48h increased b-cell proliferation 4-fold.

Conclusion- ER stress early in life inhibits postnatal β-cell proliferation burst by reducing the expression of transcription factors required for proliferation and maturation, resulting in insulin deficiency and glucose intolerance, which develop to diabetes during adulthood. These findings may have important implications for the pathophysiology and treatment of T1D and T2D.

CB1 Receptor Mediates Renal Lipotoxocity via AMPK Signaling

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Background: Recently, more attention has been given to obesity-related renal structural and functional changes, which develop early in the course of obesity. While activation of the cannabinoid-1 receptor (CB_1R), expressed in numerous cell types in the kidney, plays an important role in the onset of nephropathy, its blockade improves renal function in different animal models of obesity. However, whether these effects are mediated via a specific cell type within the kidney is still unknown.

Aim: To delineated the pivotal role of CB_1R in the renal proximal tubular cells (RPTCs) in mediating the deleterious effects of obesity on the kidney.

Methods: We developed and characterized a novel mouse strain that lacks CB_1R in the RPTCs, and determined its metabolic and renal profiles under standard or high-fat diet (HFD) feeding. In addition, we defined the downstream signaling pathway invovles in the activation/blockade of CB_1R in the RPTCs.

Results: When maintained on a HFD for 14 weeks, RPTC-$CB_1R^{-/-}$ mice became as obese and metabolic dysfunctional as their littermate controls. While the HFD feeding resulted in a similar increase in renal endocannabinoids in both mouse strains, the deletion of CB_1R in the RPTCs significantly attenuated the obesity-induced kidney dysfunction and injury as well as inflammation and fibrosis. These improvements were associated with increased activity of the energy sensor AMPK in the RPTCs, and reducing renal lipotoxicity.

Conclusion: Our findings demonstrate that CB_1R in RPTCs does not contribute to the metabolic effects associated with obesity. Yet, it has a key role in the pathogenesis of obesity-induced renal complications by regulating AMPK signaling. This work may support the development of tissue/cell-specific CB_1R antagonists against obesity-related chronic kidney disease.

Key words: Chronic Kidney Disease, CB_1 Receptor, AMPK

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The Effect of Vitamin D on Platelet Function in Diabetic Patients With or Without Aspirin Treatment

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Background: The leading cause of morbidity and mortality in Diabetes mellitus type 2 (DMT2) patients are cardiovascular atherosclerosis, peripheral arterial disease and cerebrovascular diseases. In order to reduce the risk of micro-vascular and macro-vascular complications in DMT2 patients, it had been shown that the value of glycated-hemoglobin (HbA1c) should be kept below 7%. The accumulation of Platelet plugs at sites of atherosclerotic lesion rupture is the most common mechanism leading to myocardial or cerebral infarction. A close association between poor glycemic control and increase platelet activity in patients with DMT2 had been described. It has also been found that in subjects with or without diabetes, HbA1c was inversely related to vitamin D level.

Aim: To study the relation of HbA1c and platelet aggregation and activity, and to evaluate the direct effect of calcitriol on platelet aggregation.

Methods: Blood samples of volunteers with different HbA1c levels were collected and stratified into 3 groups: I. HbA1c5.7%; II. 5.7%≤HbA1c≥6.4%; III. HbA1c6.4%. Platelet Rich Plasma (PRP) pre-treated with 1nM calcitriol or saline was tested for platelet aggregation, using 0.25µg/ml collagen or 1µM ADP as agonists.

Results: Diabetic patients with HbA1c6.4% and with no aspirin treatment showed increased platelet aggregation when collagen or ADP were used as agonists (73% and 60% respectively). These values were significantly higher than platelet aggregation of patients with HbA1c6.4% taking aspirin treatment (30% and 31% respectively) and of HbA1c5.7% group (40% and 30% respectively). In addition, calcitriol reduced significantly platelet aggregation of the HbA1c5.7% group by 21% and of the HbA1c6.4% group by 22%, compared to saline.

Conclusions: Our results show that HbA1c higher than 6.4% is related to high platelet aggregation, and this phenomenon is decreased by aspirin. Moreover, we demonstrate a novel role for calcitriol as it directly affect platelet and reduces their aggregation.

A genetic defect of the mitochondrial energy supply: characterization of a novel NDUFAF5 mutation

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Background: Mitochondrial dysfunction is a contributor to β-cell failure in type-2-diabetes. The Cohen-diabetic-sensitive rat (CDs) is a unique model of mitochondrial-respiratory, complex-IV deficiency, developing hyperglycemia when fed a diabetogenic-high-sucrose, copper-deficient diet (DD). Copper is a key-element for the catalytic activity of complex-IV. *NDUFAF5* (NADH:Ubiquinone Oxidoreductase-Complex-Assembly-Factor-5) gene, encodes a mitochondrial complex-I assembly-factor which was associated with Complex I & IV deficiencies in Leigh-syndrome patients.
Aim: We examined Complex-I and complex-IV activity in islets and fibroblasts in relation to progression to diabetes in CDs-rats attempting to elucidate the genetic-basis of their β-cell dysfunction.
Methods: Blood-glucose and insulin-concentrations were measured before and during OGTT performed at different periods on a DD or a copper-supplemented-DD. Islets and fibroblasts complex-I and complex-IV activity were measured spectrophotometrically. Whole-genome sequencing was performed in blood-DNA using Illumina HiSeq2500 followed by in-silico variant-analysis. Protein-levels were determined by Western-blot and supercomplex assembly by BN-PAGE. Rescue experiments were conducted by lentiviral-vector overexpression of a
wild-type *NDUFAF5*-gene, in CDs primary-fibroblasts.
Results: We found a highly significant positive correlation between complex-IV activity and glucose-stimulated-insulin-secretion and an inverse-correlation with blood-glucose-levels (R^2=0.984 and R^2=-0.915, P0.0001 respectively) in islets of CDs fed DD or copper-supplemented-DD. Complex-I activity was 30% reduced in CDs-islets relative to the control-islets (P0.01). Whole-genome-sequencing identified a novel homozygous missense variant, p.P318L (c.C1002T), in the *NDUFAF5*-gene predicted to be highly pathogenic by in-silico tools. *NDUFAF5* protein level was significantly decreased (P0.01) in CDs-islets compared to control-islets. BN-PAGE demonstrated reduced complex-IV supercomplex-assembly in CDs-islets (P0.01). Overexpression of wild-type *NDUFAF5*-gene in CDs-fibroblasts increased both complex-I and complex-IV activity (P0.01).
Conclusions: Our results demonstrated a tight correlation between impaired mitochondrial function and β-cell dysfunction in CDs, a model of mitochondrial-disorder related diabetes. The identified novel homozygous missense variant, p.P318L in the *NDUFAF5*-gene may underlie the CDs-mitochondria defect and susceptibility to develop diabetes.

Quantitative Proteomics Of Rat Livers Shows That Unrestricted Feeding Is Stressful For Proteostasis With Implications On Life Span

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Introduction: Children malnutrition, is considered a leading cause for growth attenuation and failure to thrive; catch up growth (CU), bringing the child back to its original growth trajectory, is considered a success of treatment. However CU growth may be associated with increased propensities to develop metabolic complications in late adulthood; food restriction (RES) in adults is the most accredited treatment against aging, associated with attenuation of a large spectrum of age-associated diseases (diabetes, immune dysfunction and Alzheimer).

Aims and methods: we used high-throughput MS quantitative proteomic analysis of whole rat livers to identify the major qualitative and quantitative changes in liver protein profiles of *ad libitum*, food restricted- and re-fed rats; to address the molecular basis for growth arrest and the apparent life-prolonging phenotype of RES regimen.

Results: Over 1800 common proteins were significantly quantified in the livers, (92% of the total protein mass). Interestingly, the very slow growing RES liver cells massively accumulated specific mitochondrial proteins while ad libitum cells contained significantly less mitochondrial catabolic enzymes and more cytosolic and ER chaperones (HSP). Following re-feeding, levels of HSPs nearly reached ad libitum levels.

Conclusions: The elevated levels of HSP-chaperones in *ad libitum* tissues were characteristic of chronic heat- and chemically-stressed tissues, which in the long term could lead to early aging and shorter life span. Proteomic values showed that although massive protein synthesis is required for rapid growth of the young animals, when sustained, this brings upon a continuous strain on the protein quality control machineries, which could lead in the long term to the formation of toxic protein aggregates ultimately reducing life span. The quantitative and qualitative protein values indicated that the restriction regimen was a least stressful condition that used minimal amounts of HSP-chaperones to maintain optimal protein homeostasis and sustain optimal life span

Oral Presentations: Reproduction

The Role of Hyaluronan during Blastocyst Attachment in Mice

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Mammalian pregnancy comprises a number of discrete and essential events including implantation, decidualization and placentation culminating in the birth of a healthy offspring. However, in humans, 75% of the abortive pregnancies are attributed to implantation failure. Successful embryo implantation requires the fulfillment of highly synchronized processes at the feto-maternal interface that precede post-implantation development, including apposition of the blastocyst and its attachment to the endometrial epithelium followed by its invasion into the uterine wall. Hyaluronan, a large negatively charged oligosaccharide, is a major ECM component known to regulate numerous adhesion-associated biological processes in a number of physiological settings. Therefore, we hypothesized that the adhesive properties of hyaluronan facilitate blastocyst attachment in mice. In order to test the role of hyaluronan during attachment, we have generated mouse transgenic blastocysts, in which genes encoding for hyaluronan synthesizing enzymes were deleted by lentiviral incorporation into the embryonic trophectoderm. Histological analysis revealed impaired implantation at E4.5. In addition, uterine flushing of pregnant mice uteri revealed decreased attachment of mutated embryos, a notion that was further supported by decreased attachment rates of mutated blastocysts to human uterine epithelium cells, *in vitro*. Functional MRI inspections revealed decrease in uterine blood vessels permeability, which constitute the immediate response to blastocyst apposition in mice. Taking these observations into account, we suggest that hyaluronan excreted by the trophectoderm plays an essential role at the feto-maternal interface, during the attachment of blastocysts to uterine epithelium.

Vasorin is a newly Identified Regulator of Ovarian Folliculogenesis and Ovulation

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The ovary is a dynamic organ, comprised of follicles at different developmental stages, the earliest of which are primordial follicles (PMF). Most of the PMF are kept dormant and constitute the ovarian reserve whereas only a selected population is activated for continues development, a process known as folliculogenesis. Regulation of folliculogenesis involves several members of the TGFβ superfamily. Vasorin (Vasn) is a newly identified negative regulator of the TGFβ signaling pathway. We aimed at elucidating the role of Vasn in ovarian physiology. Using qPCR and in-situ hybridization we identified, for the first time, the expression of Vasn in ovarian granulosa cells of primordial, primaty, secondary and antral mouse follicles. Furthermore, Vasn expression in preovulatorty follicles is up-regulated by LH. VASN protein expression, shown by immunohistochemistry (IHC) and ELISA, exhibits a similar LH-induced pattern. In order to understand the physiological role of Vasn, we generated Vasn conditional KO (cKO) mice, directed selectively to the granulosa cells using Cyp19-Cre recombinase. We found that the number of oocytes stimulated to ovulate by exogenous hormonal treatment, was almost two-fold higher in cKO mice as compared to their WT siblings . In addition, TUNEL staining revealed a lower level of atresia in antral follicles of the cKO mice . IHC of pSmad2 confirmed the TGFβ signaling pathway is over-activated in ovaries of cKO mice. Finally, we found a decreased ovarian reserve in pre-pubertal cKO mice, suggesting that Vasn, which is secreted by growing follicles, protects the ovarian reserve. Our results reveal Vasn as a new central player in folliculogenesis, which is involved in regulation of the size of ovulation and the maintenance of the ovarian reserve. We intend to further examine the mechanism by which Vasn elicits its action and test its potential role in human folliculogenesis.

The role of Pigment epithelium-derived factor (PEDF) in the pathogenesis of PCOS

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PCOS is the most common endocrine disorder in women at the reproductive age; associated with reproductive, endocrine, metabolic, angiogenic and systemic inflammatory features. Women with PCOS present elevated androgens as well as increased production and secretion of ovarian vascular endothelial growth factor (VEGF) and cytokines (interleukin (IL)6; IL8). Overproduction of VEGF and IL6\8 after gonadotropin stimulation, is considered responsible for the development of ovarian hyper-stimulation syndrome (OHSS), frequently seen in PCOS patients. We have shown that PEDF, a potent anti-angiogenic (VEGF) and anti-inflammatory (cytokines) factor plays fundamental role in OHSS pathogenesis and treatment. We have also demonstrated, in a model of PCOS-mice, that the level of ovarian VEGF increases whereas that of PEDF mRNA decreases. Our aim is to elucidate the ovarian anti-inflammatory role of PEDF and its relevance to PCOS pathogenesis.

The *in-vitro* part was performed in cultures of human primary granulosa cells (hpGC) isolated from follicular fluids aspirated from woman undergoing IVF.

The level of IL6 and IL8 mRNAs increased in lysophosphatidic acid (LPA 10uM)-stimulated hpGCs. Co-stimulation with recombinant (r)PEDF (5nM) decreased the LPA-induced expression of IL6/8 mRNAs (P0.05). However, GW (specific inhibitor of Peroxisome proliferator-activated-receptor-gamma; PPAR-γ) abolished the anti-inflammatory effect of rPEDF in rPEDF-and LPA-stimulated cells, suggesting that the anti-inflammatory effect of PEDF in granulosa cells involves the PPAR-γ pathway. hpGC stimulated with dihydrotestosterone (10ng/ml) exhibited significant increased expression of IL6 and IL8 mRNAs, which was restrained (P0.05) by co-stimulation with rPEDF. Stimulation of hpGC with IL8 increased VEGF mRNA expression; whereas co-stimulation with rPEDF diminished it (P0.04). The level of PEDF mRNA was downregulated by stimulation with dihydrotestosterone (70%) and (50%; P0.001).

Our findings suggest that low level of ovarian PEDF lies at the core of PCOS pathogenesis where the impaired angiogenic/inflammatory balance, induced by increased levels of androgens and cytokines, can be restored by PEDF.

PKA and EPAC signaling mediate prostaglandin E2/EP2 receptor-induced epiregulin and FGF2 in granulosa cells.

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Introduction: PGE2, epiregulin (EREG) and FGF2 are elevated in the early corpus luteum (CL) immediately after ovulation. Although LH is known to stimulate these factors, their expression is also interdependent. For instance, PGE2 induces EREG and other EGF-like peptides. Classically PGE2 acts via cAMP but its detailed mechanism of action is still unclear.

Aim: Examine whether PGE2 can induce FGF2 along with EREG and elucidate the signaling pathways involved in their expression in granulosa cells (GCs).

Methods: GCs from large healthy bovine follicles were treated with: PGE2; PD173074 (FGF-receptor inhibitor); PGE receptor agonists (EP1-4); H-89-dihydrochloride (protein kinase A (PKA)-inhibitor); 8-(4-Chlorophenylthio)-2'-O-Me-cAMP-AM (exchange-protein directly activated by cAMP (EPAC)-activator); ESI09 (EPAC-inhibitor) and ESI05 (EPAC2-specific-inhibitor). GCs were transfected with scrambled/prostaglandin-endoperoxide-synthase2 (PTGS2) siRNA. Viable GCs numbers, mRNA and protein levels were measured by XTT, qPCR and western blotting, respectively.

Results: PGE2 maximally induced FGF2 and EREG at 3hr decreasing gradually until 24h. Similarly, knocking-down PGE2 levels in PTGS2-silenced GCs, exhibited low FGF2 and EREG. PGE2 induced FGF2 protein and increased viable GCs' numbers. PD173074 significantly abolished this last effect, thus verifying that PGE2 affects GCs' survival via FGF2. Amongst four EP agonists, only EP2 agonist (butaprost) mimicked PGE2 effect on FGF2 and EREG. To check the involvement of PKA, a canonical downstream target of cAMP, H89 was used. With this inhibitor EREG stimulation was abolished while FGF2 remains unchanged. FGF2 stimulation was EPAC -dependent: EPAC activator upregulated FGF2 but also EREG. FGF2 was inhibited by EPAC1 inhibitor while EREG was partially reduced by EPAC2 inhibitor.

Conclusions: This study highlights a new role and mechanism of PGE2 action in GCs. PGE2 upregulated FGF2 and EREG via EP2 subtype. Interestingly, while FGF2 expression was EPAC dependent, EREG was mediated by both PKA and EPAC. These results demonstrate the diverse functions of PGE2 in CL development.

Normal Androgens Levels During Singleton Pregnancy in Healthy Women

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Background: Knowing the androgen levels during normal pregnancy will enable better adjustment of glucocorticoid dosage during pregnancies of females with congenital adrenal hyperplasia. The current norms for singleton pregnancies were published between the 70's and 90's,

Aim: To assess the normal androgen levels for each pregnancy trimester in singleton pregnancies with current laboratory methods.

Setting: Endocrinology Specialty Clinic and Endocrine Laboratory at a tertiary teaching hospital.

Subjects and Methods: Healthy pregnant women were asked to participate. Blood was drawn during each trimester and postpartum for the assessment of 17OHP, androstenedione and testosterone levels and the 3rd and 97th percentiles were generated.

Results: 52 women aged 33.4±3.0 years were recruited prospectively. Their mean age of menarche was 12.7±1.0 years and their mean body mass index was 21.4±3.4. The mean first trimester 17OHP level was 7.62±4.95nmol/l, androstenedione 9.21±5.06nmol/l, and testosterone 1.67±1.15nmol/l. The mean second trimester 17OHP level was 6.72±3.75nmol/l, androstenedione 10.99±5.09nmol/l, and testosterone 1.80±1.70nmol/l. The mean third trimester 17OHP level was 12.30±5.64nmol/l, androstenedione 14.83±4.54nmol/l, and testosterone 2.15±1.49nmol/l. For comparison, the established mean normal non-pregnant 17OHP level is 2.16±1.92nmol/l, androstenedione 3.84±2.09nmol/l, and testosterone 0.38±0.31nmol/l. Comparison between the different trimesters for each hormone revealed significant differences between the second and third trimesters for 17OHP ($p0.001$) and androstenedione ($p=0.015$). There were highly significant differences between each trimester of pregnancy and non-pregnant levels of all three hormones ($p\leq0.001$).

Conclusions: We provide normal levels of 17OHP, androstenedione, and testosterone for each trimester of singleton pregnancy. As expected, these levels were significantly higher than non-pregnant levels. To further validate these norms, a larger cohort should be studied and twin pregnancies should be evaluated as well. Meanwhile, these norms can be used as references for pregnant women being treated for congenital adrenal hyperplasia.

Anti-Mullerian Hormone serum levels remain stable under cross-sex hormone therapy of transgender men

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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 IM Testoviron Depot 250 mg q3 weeks. Sampling was conducted in the follicular phase at baseline and 10 days following the testosterone injection three and 12 months subsequently.

Main outcome measures: AMH serum levels; endometrial thickness and antral follicular count determined by pelvic US.

Results: Thirty five subjects (mean age 24±5.9 y) were included. Preliminary results of twenty two patients with at least one follow up visit are reported.

AMH levels were within the normal range (5.8±2.9 ng/ml) and did not change significantly after three (5.3±2.4 ng/ml, N=22) and 12 months of treatment (4±2.2 ng/ml, N=8). As expected, testosterone levels increased (0.57 ± 0.7, 6 ±3.2 ,6.6 ±2.8 ng/ml; p0.0001) and estradiol levels decreased (187±184 , 57±15, 54.8 pg/ml; p=0.012) after three and 12 months respectively. There was a modest but significant decrease in LH levels (7.7±5, 4.2±3.4, 3.9 ± 2.8 mIU/ml, p=0.022), but FSH levels (4.1±1.7, 4.4±2.2, 4.7±1.8 mIU/ml), as well as endometrial thickness (7.2±3.9, 5.3±1.2, 5±3.3 mm) remained unchanged. In all but two studies, multiple ovarian small follicles were detected by pelvic sonography.

Conclusion: AMH levels remain stable during short term testosterone treatment. Further, there is no suppression of the hypothalamo-pituitary-gonadal axis and ovarian folliculogenesis is maintained. Longer follow up is needed for assessment of testosterone effects on fertility potential.

Plenary lecture 1:

Polycystic Ovary Syndrome and Risks for Diabetes and Cardiovascular Disease: Therapeutic Implications

John E. Nestler
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The polycystic ovary syndrome (PCOS) is a prevalent disorder affecting at least 5-10% of women of childbearing age. It is classically characterized by chronic oligo- or anovulation and androgen excess (clinical or biochemical). Abundant evidence indicates that the majority of both lean and obese women with PCOS are markedly insulin-resistant above and beyond that expected for body mass index. This insulin resistance places women with PCOS at high risk for comorbidities such as type 2 diabetes and premature cardiovascular disease. Evidence indicates that 30-50% of obese women with PCOS develop glucose intolerance (either impaired glucose tolerance or type 2 diabetes) by the age of 30 years. Women with PCOS also demonstrate a higher prevalence of cardiovascular risks factors and the metabolic syndrome, and studies have demonstrated both functional and anatomic cardiovascular abnormalities in young lean women with PCOS. Recently, a prospective study reported that postmenopausal women who had PCOS in their youth experienced a 2-fold higher cardiovascular event rate than similarly aged control women, and that the events occurred at an earlier age in the women with PCOS.

These considerations are important in the evaluation and long-term medical management of women with PCOS. Once a diagnosis of PCOS has been established, at a minimum, a 2-hour oral glucose tolerance test and lipid profile should be obtained. Studies comparing the metabolic effects of oral contraceptive pills versus the insulin-sensitizing drug metformin suggest that the latter is more effective in addressing the comorbidities of PCOS and is therefore useful in the long-term management of PCOS.

Laboratory Definition of Hyperandrogenism and its Pathogenesis

Renato Pasquali
University Alma Mater Studiorum of Bologna, Italy

PCOS is the most common hyperandrogenic disorder, with a high prevalence of metabolic c-omorbidities, including obesity, insulin resistance and the metabolic syndrome. We are facing the need to change our perspective in defining PCOS. In fact, thanks to the advance in measuring blood androgen levels by LC-MS/MS, it has become clear that almost all typical cases of PCOS have a variable pattern of androgen excess which, in turn, is likely to play an important role in determining associated metabolic abnormalities. In addition, there are arguments to support the concept that in many patients a secondary form of PCOS related to obesity may exist, particularly when it develops during adolescence. Additional mild phenotypes may have different pathophysiological mechanisms. As for other endocrine syndromes, we should therefore consider that PCOS, precisely because it is a "syndrome", may include many different phenotypes, ranging from the classic forms to milder ones, and that, in addition, a secondary PCOS may occur

Symposium 1: PCOS

The Impact of Carbohydrate-Poor Diet of Gut Microbiome of Women with PCOS

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The polycystic ovary syndrome (PCOS) has long been known for its association with body weight and nutrition. The earliest records already indicated that dietary modification and weight loss are corrective. In the last two decades it became clear that individual ovarian androgenic responsiveness to blood levels of insulin is the key feature of this syndrome. The last decade has seen an explosive development in the study of gut microbiome (GMic), made possible by mass sequencing of genomes and computerized analysis of results, which indicates a clear association of certain disease states with specific GMic profiles. Furthermore, the GMic is now recognized as a central participant in the total body metabolism and immunity of the host organism and the relations of the two are mostly characterized by the term "cross-talk". It is also recognized that dietary change induces changes in the microbiome's composition. Our clinical experience, as well as controlled studies of others, indicated to us that even lean PCOS patients can benefit from a diet poor in carbohydrates. Furthermore, we found that even these lean women have a clear preference to a diet rich in carbohydrates. It was thus tempting to speculate that PCOS patients have a deviant GMic and that dietary change should have an impact on their GMic, probably bringing it closer to GMic of ovulatory women. We indeed found that PCOS patients have a characteristic GMic composition, which is different from that of ovulatory controls. We also found that two months of a diet poor in carbohydrates induced a change in the patients' GMic that brought its composition closer to that found in ovulatory controls. Some patients did not complete the course of diet for the study because they conceived earlier than two months. Detailed results will be presented during the meeting.

Distinct Hypoxic Responses in PCOS-Derived Granulosa Cell

Rina Meidan
The Hebrew University

Endothelin-2 (EDN2) is essential for the ovulatory process. To better understand the mechanism regulating its expression in human granulosa-lutein cells (hGLCs), we studied how hypoxia and microRNA-210 (miR-210) affect *EDN2*. These *in vitro* data were corroborated by comparing cells derived from normally ovulating women with those of polycystic ovary syndrome (PCOS) women having anovulatory infertility. We found that miR-210 and *EDN2* were closely related in hGLCs: i) hypoxia and miR-210 overexpression both increased *EDN2*, whereas miR-210 inhibition reduced it, ii) HIF1A-silenced cells, previously shown to have reduced *EDN2*, also exhibited significantly lower levels of miR-210 and iii) GLCs from PCOS had significantly less miR-210 and *EDN2* as compared to control women. Two molecules that destabilize HIF1A protein were examined (glycerol-3-phosphate dehydrogenase 1-like gene-*GPD1L*, and succinate dehydrogenase subunit-D -*SDHD*). miR-210 overexpression diminished their expression, also hypoxia-elevated endogenous miR-210 reduced *GPD1L*, confirming that *SDHD* and *GPD1L* are miR-210 targets in GLCs. Lowering *GPD1L* either by miR-210 overexpression or siRNA knockdown resulted in elevated HIF1A protein and *EDN2* levels. hGLCs from PCOS had higher levels of *GPD1L* and *SDHD*. Altogether, data from PCOS strongly support the in vitro experimental results. Our findings suggest a positive feedback loop in hGLCs, where miR-210 induced by hypoxia (via HIF1A) lowers *GPD1L*, which acts to further maintain HIF1A protein levels. This feed-forward loop is expected to augment *EDN2* in cells exposed to hypoxic conditions during ovulation. Conversely, reduced miR-210 in PCOS might interrupt this loop, thus decreasing *EDN2* expression contributing to impaired ovulation and abnormal CL formation.

Symposium 2: Obesity and Metabolism

Circadian Clock Control of Metabolism

Gad Asher
Department of Biomolecular Sciences, Weizmann Institute of Science

Circadian clocks are positioned at the cross road between nutritional cues and metabolic control. Thus, studying metabolism from a temporal and spatial perspective provides a unique niche that is expected to unveil novel fundamental principles related to basic metabolism and their nutritional control. In recent years my lab employed different methodologies, from biochemical approaches that identify protein-metabolite interactions through measurements of metabolic outputs in intact cells and living animals to high-throughput proteomics and metabolomics, to examine temporal and spatial aspects of metabolism. During my talk, I will discuss several examples emerging from our work on different groups of metabolites (e.g., lipids, polyamines) and on cellular metabolic processes (e.g., mitochondrial function) that shed new light in respect to their temporal and spatial intracellular organization and their nutritional control by different dietary regimens.

Leptin and Lipodystrophy

Talia Diker-Cohen
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Lipodystrophies are rare disorders of subcutaneous fat loss, leptin deficiency, severe insulin resistance and hypertriglyceridemia. Conventional treatment of hyperglycemia and hypertriglyceridemia does not achieve adequate control of lipodystrophy patients. Leptin replacement therapy was FDA-approved in 2015 for generalized lipodystrophy, but not for partial forms due to uncertain benefit.

A multi-society practice guideline has recently been published in the Journal of Endocrinology and Metabolism to guide physicians on the approach to diagnosis and treatment of lipodystrophy.

An overview of the diagnosis and classification and leptin treatment in lipodystrophy will be presented to increase the awareness to this rare and probably underdiagnosed group of disorders

Plenary Lecture 2:

Decoding Obesity - Control of Metabolism by the Noncoding Genome

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MicroRNAs are critical regulators of liver metabolism and adipose tissue plasticity; *in vivo* administration of inhibitors against obesity-associated microRNAs represents a novel therapeutic approach which ultimately can succeed in improving metabolic disease in mice and, potentially, humans.

In addition to microRNA, another class of noncoding transcripts termed long noncoding RNAs (lncRNAs) governs energy homeostasis and metabolic flexibility during health and metabolic disease. Intriguingly, using Next-Generation Sequencing and novel systems -OMICS approaches, our group has observed that glucose intolerance and insulin resistance in two independent mouse models of obesity are coupled to global repression of lncRNAs in liver, whereas protein-coding genes are not affected. The same was found in liver biopsies from diabetic human patients.

Analyses of *in vivo* transcriptomic datasets and computational DNA motif prediction algorithms revealed that lncRNAs, in contrast to coding genes, harbor conceptually different promoter regions that serve as specific docking platform for an inhibitory class of transcription factors termed smallMaf proteins. In line with this, an obesity-associated rise in smallMaf signaling is seemingly involved in the global demise of lncRNAs during metabolic disease. Crucially, we could delineate that this newly identified smallMaf-lncRNome signaling axis also controls glucose and lipid homeostasis, suggesting for the first time that system-wide energy states (fasting, refeeding, and obesity) are coupled to noncoding transcription, presumably via distinct signaling cascades like the smallMaf pathway.

Symposium 3: Transitional Endocrinology "Tips from the Pediatric to the Adult Endocrinologist"

Combined Pituitary Hormone Deficiency (CPHD): Important Issues from Infancy to Adulthood

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CPHD is characterized by the impaired production of GH and one or more additional pituitary hormones. The initial presentation is fasting episodes of hypoglycemia in infancy and growth retardation in the first year of life. The etiology is divided into congenital and acquired causes. The congenital etiologies are divided into syndromic and non-syndomic CPHD. Commonly, the syndromic cases are attributed to early acting pituitary transcription factors whereas the non-syndromic to late acting transcription factors. To date, more than 20 genes were identified attributed to abnormal pituitary development and they explain only 10-30% of the genetic etiologies. NGS is the method recommended for gene analysis but the role of genetics in the diagnosis of CPHD yet remains to establish. Deficiency of hormones may developed with time therefore, long term and repeated laboratory evaluation is recommended. Auxologic based GH dosing is the recommended approach for GH therapy. Until the last years, GH was regard as safe medication but recently, higher potential risk for early mortality was reported in adult previously treated with GH. The aims of GH therapy in transition and in adulthood are for improving body composition, exercise capacity, skeletal integrity, quality of life and cardiovascular function. To confirm the diagnosis of GHD in patients with CPHD in transition, GH stimulating tests are unnecessary. Recent studies suggest that patients with IGF-I deficiency has advantage of longer lifespan and less cancer morbidity. It has been suggested that humanin, mitochondrial anti-oxidant protein, negatively correlate with IGF-I, are associated with extended longevity. Based on the current knowledge, the final decision to treat adults with GHD requires thoughtful clinical judgment with a careful evaluation of the benefits and risks.

Disorders of Gonadal Differentiation

, Mariana Rachmiel
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Transition has been defined as 'the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems'. The transition process of endocrine patients from the paediatric to adult setting is still suboptimal, especially in patients with complex disorders. Furthermore, there is evidence that the process of transition from paediatric to adult health services is often associated with deterioration in the health of adolescents with chronic conditions.

Sometimes it is difficult for young people to detach emotionally from their paediatric endocrinologist and/ or the abrupt change from an environment of parental responsibility to autonomy. It appears endocrine patients need more tailored care to prevent complications like failure to achieve bone mineral density, morbid obesity, metabolic perturbations, inappropriate/inadequate puberty, compromised fertility, diminished quality of life and failure to adapt to the demands of adult life.

The medical term disorders of sex development (DSDs) is used to describe individuals with an atypical composition of chromosomal, gonadal and phenotypic sex, which leads to differences in the development of the urogenital tract and reproductive system. Treatment of patients with DSDs include variable endocrine and surgical options, with many concerns as to which and when is the best treatment option. Recently, it had been emphasized that dealing with DSDs requires acceptance of the fact that deviation from the traditional definitions of gender is not necessarily pathologic, and the transition to adult world may be a critical period of time for those and other psychobehavioral issues to be discussed.. This period is the ideal time for patients with DSD to be made aware of their health history and health needs and of the evolving impact into adulthood.

The purpose of the talk is to highlight the importance of an improved, seamless, and effective transition from pediatric to adult care, especially for medically complex conditions such as DSD, including Turner syndrome. It is the medical care team task to ensure continuum of care and optimal treatment outcomes, optimizing adult health and longevity.

Symposium 4: Current Topics in the Endocrine Labs - What Clinicians Should Know

Diagnosis and Evaluation of The Hypertensive Patient and the Use of Aldosterone/Direct Renin Concentration Ratio

Yehonatan Sharabi
מנהל המכון ללחץ דם, המרכז הרפואי שיבא, תל השומר ואוניברסיטת תל-אביב

ב- 1954 תיאר ג'רום קון לראשונה אישה צעירה עם חולשה אפיזודית, ספאזם שרירי, וממצא של לחץ דם גבוה, אשלגן נמוך, נתרן גבוה ואלקלוזיס. מהיותו מומחה ל"מלח וזיעה" הוא הציע שמדובר בעודף קורטיקוסטרואידים. מאז פרסום זה הצטבר ידע רב על היפראלדוסטרוניזם וההסתמנות נעה בין אדנומה מפרישה אלדוסטרון (תסמונת קון), עבור דרך היפרפלזיה. דו-צדדית בדרך כלל, של האדרנלים ועד מקרים נדירים של גידולים פונקציונליים של האדרנל שמפרישים אלדוסטרון. תשומת הלב למצב זה נובעת מהיות המצב של היפראלדוסטרוניזם גורם שכיח בקרב אלו עם יתר לחץ דם שניוני או עמיד לטיפול והעובדה שבירור מושכל יכול להביא לאבחנה ברורה וטיפול (תרופתי או כירורגי) יעילים.

החשד הקליני צריך להתעורר גם אם אין את הסימנים והתסמינים הקלאסיים שתיאר ג'רום קון. די בלחץ דם עמיד לטיפול או אשלגן בטווח הנמוך של הנורמה כדי לשלוח לבדיקת סקירה. היום, מדידות רנין ואלדוסטרון בפלזמה קלים לביצוע, בעיקר בזכות האפשרות לבצע מדידה ישירה של רנין, ולא השיטה העקיפה – שהתבססה על קביעת פעילות האנזים.

מעבר לבדיקות הסקירה, אישוש מעבדתי, כמו במבחן העמסת סליין, והדמיה מכוונת לאדרנל (CT קודם בלי ואח"כ עם חומר ניגוד או .MRI והוכחה סופית לכך שיש אדנומה המפרישה אלדוסטרון (ע"י דיגום ורידי אדרנל) מאפשרים להגיע לאבחנה ברורה במרבית המקרים.

הטיפול מותאם אישית, כשנלקחים בחשבון משך המחלה, תגובה לטיפול תרופתי ועוד ביומרקרים מנבאים לתגובה לטיפול כירורגי במידה ומדובר באדנומה מפרישה או היפרפלזיה חד-צדדית. לחילופין, טיפול תרופתי הבולם קולטני אלדוסטרון, ובעתיד הלא-רחוק – מעכבי אלדוסטרון סינטאז, מאפשרים, כמעט תמיד, טיפול יעיל ואיזון לחץ הדם ומניעת סיבוכיו ששכיחים במיוחד כשהרקע הוא היפראלדוסטרוניזם.

Mass Spectrometry-Based Metabolomics: Application to Adrenal Diseases and More

Elena Dumin
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The steroid metabolome is best understood by analogy to the genome, i.e. where the genome is the set of all genes in a human, the steroids metabolome is the set of steroids metabolites in a given individual. Every human being has his particular steroid metabolome. Similarly, every adrenal or gonadal disease or disorder has its characteristic pattern of steroid metabolites. Steroid profiling is ideal for detection of altered steroid metabolism, due to defects in steroidogenic enzymes however up to date this profiling is available only in a few clinical laboratories in the world.

In this session, the physical principles of mass spectrometry (MS), the terminology used in this field and some interesting clinical cases will be presented.

Urinary steroid profiling by Gas Chromography (GC) and Gas Chromography –Mass Spectrometry (GC-MS) provides qualitative and quantitative data on excretion of 31 urinary steroid metabolites, as a merged picture of major biosynthetic and catabolic pathways. This technique ensures the highest specificity and accuracy in the determination of the steroid metabolites, and offers the opportunity of evaluating the Total Steroid Metabolome, which confers to it powerful diagnostic possibilities. There is no better mode of diagnosing and monitoring the enzymatic defects of biosynthesis of steroids. Almost all known inborn errors of steroid metabolism can be readily identified in a single steroid profile since the product/substract for the following enzymes activities can be tested-3β-Hydroxysteroid dehydrogenase, 21 Hydroxylase deficiency, 5α-Reductase deficiency, 11β-Hydroylase deficiency, Corticosteroid 11-dehydrogenase deficiency & Corticosteroid-11-oxoreductase deficiency, 17, 20-Lyase deficiency, Cytochrome P450 oxoreductase (POR) deficiency and more.

In addition, the amount and quality of information obtained with this methodology is so rich and unique, that it allows the diagnosis of a number of diseases which to date have resisted accurate diagnosis (the Apparent Mineralocorticoid Excess Syndrome- AME will be described in this lecture).

National Project to Determine 11-Deoxycortisol Reference Range in the Israeli Population

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11-Deoxycortisol assay is used primarily for the diagnosis and follow-up of Congenital Adrenal Hyperplasia (CAH) due to 11-hydroxylase deficiency. Most of the endocrine laboratories in Israel use a DiaSource RIA kit (Reference range: 0 - 7ng/ml or 0-21 nmol/L). Lately the manufacturer announced that the units of the published reference range are incorrect due to a typing mistake, and as a result the recommended reference values should be 0 -7 nmol/L. However, when screening thousands of results obtained in all Labs in the last few years, this change in units apparently increased the percentage of pathological results from 3% to about 40%. Since 11-hydroxylase deficiency is not common disease (prevalence 1-5% in CAH patients), both Lab Experts and the Cliniciants agreed that this rate is clinically unreasonable.

Therefore, we undertook the mission of determining the correct reference range for 11-Deoxycortisol in the pediatric and adult Israeli population. Three Endocrine Laboratories participated in the process: Maccabi-Healthcare-Services, Clalit-Health-Services Haifa region and Sheba Medical Center.

This multi-center study, redefined the reference range of 11-Deoxycortisol in the Israeli population using DiaSource RIA kit. According to this study, pediatric (in both age groups) and adult values are very similar. We determined that the appropriate reference range of the Israeli population is 4-16 nmol/L (2.5-97.5 percentiles), and these values are not compatible with DiaSource recommendations (0 -7nmol/L).

This study demonstrates that collaboration between laboratories, clinicians and professional societies can lead to national projects to determine appropriate reference range of different tests for the local population.

Biotin Treatment Can Cause Misleading Hormones Results

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Immunoassays are subjected to different interferences that may result in false results, leading to unnecessary clinical investigations and treatment.

Recently, several cases were reported of abnormal results of thyroid function tests obtained worldwide in patients that were treated with Biotin. Biotin is used as dietary supplement and for treatment of several metabolic disorders, including mitochondrial disorders and multiple sclerosis.

In this presentation, clinical examples will be described for biotin interference in the determination of different hormones, using immunoassays based on biotinylated antibodies/analogs and the laboratory basis for this interference will be discussed. The multiple steps that were undertaken to increase the awareness of clinicians and laboratory experts to this interference will be described. Awareness of both the clinicians and Lab staff are extremely important to avoid unnecessary investigations and treatment.

Influence of Meal Timing on Clock Gene and Ampk mRNA expression and Glucose, Insulin and intact GLP-1 Response after Lunch in Type 2 Diabetes

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Aim: Asynchrony of clock genes expression is associated with deficient insulin secretion, muscular glucose uptake, insulin resistance, type 2 diabetes and increased HbA1c. Meal timing not aligned with the circadian clock i.e. breakfast (B) skipping and/or eating at hours assigned to sleep, have been associated with high HbA1C and postprandial hyperglycemia. Our aim was to explore the effect of B consumption or omission on glucose homeostasis and clock gene, *Ampk*, and *Sirt* mRNA expression in type 2 diabetes (T2D).

Methods: In crossover design, 18 T2D with 14.5±1.5yr diabetes, BMI 30.7±1.1 kg/m2 and HbA1C: 7.6±0.1% were randomly assigned to a test day with B and lunch (YesB) and a test day with only lunch (NoB). Postprandial clock genes (*Clock*, *Bmal1, Per1, Per2, Cry1*, *Rev-erbα, Rorα*) Ampk and Sirt1 mRNA expression, in white blood cells (WBC), and plasma glucose, insulin, intact glucagon-like peptide-1 (iGLP-1) and dipeptidyl peptidase IV (DPP-IV) plasma activity were assessed after B and lunch.

Results: Compared to NoB day, YesB day led to 26% upregulation of Bmal1, the positive loop of clock gene expression (p0.005), to 34-43% upregulation of Ampk, Per1, Cry1 and Rev-erbα (p0.005) and to -30% downregulation of negative feedback loop Per2 response after lunch (p0.05). YesB day was associated with reduced AUC for glucose by -18 % (p0.0001), increased AUC for insulin by 25 % and by 33% for iGLP-1 response after lunch, (p0.0001), compared to NoB day.

Conclusions: Breakfast skipping adversely affects the postprandial clock genes and Ampk mRNA expression after lunch and was correlated with reduced postprandial insulin, impaired iGLP-1 and increased glycemic response after lunch in NoB day compared to YesB day. These results suggest that intake of breakfast is important for maintaining the clock gene regulation of the overall glucose metabolism in Type 2 Diabetes.

Increased Mortality in Diabetes Patients with Intensive Glycemic Control is Found Only in Patients with Haptoglobin Type 2-2 – Paradigm Shift Towards Genetically-Determined Personalized Glycemic Targets

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Background: The optimal target of glucose and HbA1c for reducing cardiovascular events and mortality in patients with long standing diabetes is not clear. The ACCORD study found higher mortality in the tight control arm in diabetes patients with high cardiovascular risk, and several large retrospective studies have found a J shape of hazard-ratio curve of HbA1c and mortality, with the lowest mortality risk in patients with HbA1c 7.5% and higher rates of mortality in patients with lower or higher values. Haptoglobin (Hp) type 2-2 is a strong cardiovascular risk factor in diabetes.

Aims: We hypothesized that Hp type may modify the effect of HbA1c on mortality in the ADHOC study cohort, consisting of 3034 diabetes patients (285 with Hp 1-1, 1248 with Hp 2-1 and 1511 with Hp 2-2).

Results: We followed the ADHOC study cohort from 2002 to 2014 for cardiovascular events and total mortality. HbA1c distribution was similar between the Hp groups. We found a pronounced J shaped curve in patients with Hp 2-2, with the highest rates of a primary composite outcome of myocardial infarction, cardiovascular mortality and non-cardiovascular mortality in Hp 2-2 patients with HbA1c6.6%. The J curve was not found in patients with haptoglobin 2-1 and 1-1, in which HbA1c values of less than 6.6% were associated with lower occurrence of the composite outcome.

Conclusions: Our results shift current clinical paradigms in treating diabetes, suggesting a novel approach to optimize “personalised medicine” based on a genetic characteristic. Determining Hp type for each diabetes patient may be useful for making decisions on the intensity of glycemic treatment.

Therapeutic Response to Metreleptin in Childhood Onset Lipodystrophy: Experience of an Israeli Pediatric Diabetes Center

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Introduction Patients with lipodystrophy syndromes may be affected by severe metabolic abnormalities. Treatment with Leptin is currently approved in the United States for generalized lipodystrophies (GLD), but not for patients with partial lipodystrophy (PLD), as data on its effectivity in these patients is lacking. Preliminary, open label studies in partial lipodystrophies suggest a benefit in patients with severe metabolic complications.

Aim To describe the clinical experience of an Israeli Pediatric Diabetes Center in childhood onset lipodystrophy (GLD and PLD) and the therapeutic response to Metreleptin.

Patients and Methods The clinical presentation, course and outcome of 3 female patients clinically diagnosed with lipodystrophy, and one or more metabolic derangement (diabetes with insulin resistance, hypertriglyceridemia or hepatic steatosis) are presented. All patients received self-administered SC Metreleptin injections in one to two daily doses ranging from 0.05 to 0.1 mg/kg · d. Doses were adjusted to achieve metabolic control.

Results Treatment with Metreleptin resulted in a dramatic improvement in physical parameters (acanthosis nigricans and hepatomegaly) and metabolic parameters (a decline in glycated hemoglobin A1c and triglycerides, and normalization of liver transaminases). Insulin requirements decreased markedly and 2/3 patients discontinued insulin after attaining target HbA1c (6.5%). Initiation of treatment resulted in normal progression of puberty (1/3) and resolution of primary amenorrhea (2/3). No adverse events that were judged to be related to treatment occurred. Microalbuminuria was not resolved and patients required ACE inhibitors. Autoimmune co-morbidities included Hashimoto (2/3), psoriasis (2/3), positive ANA (1/3) and positive Ro (1/3). Genetic sequencing was performed in all patients.

Conclusions Based on our experience, Metreleptin is a safe and effective mode of therapy for improving the outcome of lipoatrophic diabetes and steatohepatitis in patients with childhood onset lipodystrophy. A multidisciplinary team including a pediatric gastroenterologist, endocrinologist and dietary consultant may be beneficial for providing optimal care.

Semaphorin 3E, a novel adipokine with pro inflammatory and insulin resistance properties, is positively correlated with insulin resistance in human pregnancy

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Objective: Semaphorin 3E (Sema3E), a previously known axon guiding factor in the developing nervous system, has recently been shown to be an adipokine implicated in the pathophysiology of adipose tissue inflammation and insulin resistance. The aim of this study was to determine circulating Sema3E levels and their correlation with insulin resistance indices in non-pregnant women, uncomplicated pregnant women and patients with gestational diabetes mellitus.

Methods: Fasting serum glucose, insulin and Sema3E levels were determined in 45 healthy non-pregnant women and 67 pregnant women at term (58 women with uncomplicated pregnancy and 9 women with gestational diabetes mellitus- GDMA2). The Homeostasis Model Assessment (HOMA) was used to evaluate insulin resistance. Non-parametric statistical methods were employed.

Results: In non-pregnant women, Sema3E levels were higher in lean/normal versus obese/overweight women (1.27, IQR: 0.66-1.73 ng/ml vs. 0.67, IQR: 0.45-1.11 ng/ml, respectively, p=0.02), and were negatively correlated with their BMI (r=-0.5, p0.001). Among obese/overweight women circulating maternal Sema3E levels were higher in uncomplicated pregnancy compared with non-pregnant state (1.13, IQR: 0.69-1.54 ng/ml vs. 0.67, IQR: 0.45-1.11 ng/ml, respectively, p=0.02). In pregnant women with normal gestation, maternal Sema3E levels were positively correlated with insulin resistance (HOMA-IR; r=0.31, p=0.02). Maternal Sema3E levels were significantly lower in GDMA2 compared with uncomplicated pregnancy (0.30, IQR: 0.30-0.40 ng/ml vs. 0.95, IQR: 0.58-1.56 ng/ml, respectively, p0.001).

Conclusions: To the best of our knowledge, this is the first study to report the presence of Sema3E in maternal blood. Circulating maternal Sema3E levels were positively correlated with insulin resistance in uncomplicated gestation, especially in the obese population, in which higher Sema3E levels were determined in a pregnant compared with a non-pregnant state. The unexpectedly lower Sema3E levels in patients with GDMA2 compared with uncomplicated pregnant women may indicate a down-regulation effect of exogenous insulin on Sema3E production or secretion. These findings suggest that Sema3E may play a role in metabolic adaptations to uncomplicated pregnancy as well as in the pathophysiology of pregnancy-related metabolic complications.

Wolfram syndrome type 2 : new insights into the pathophysiology and promising therapy options

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Background: Wolfram syndrome type 2 (WFS2) recently shown to be caused by CISD2/NAF-1 gene mutations is characterized by childhood GI bleeding, diabetes, and neurodegeneration with optic atrophy and hearing loss. NAF-1 suppression results in intra-mitochondrial accumulation of iron, increased ROS generation and consequently increased cellular apoptosis.

Objective: Given the lack of specific pathophysiologic based treatment in WFS2 we aimed to examine the response of patients` fibroblasts ex-vivo and 2 patients in vivo to iron chelators and antioxidants.

Patients and Methods: Skin biopsy was performed in 4 WFS2 patients homozygous for the E37Q CISD2 gene mutation. Fibroblasts were cultured and exposed to N-Acetyl Cysteine and Deferiprone Ex- Vivo. Following promising results in cultured fibroblasts, initially 2 patients were treated with N- Acetyl Cysteine 200 mg per day and Deferiprone 20 mg per kg per day for 60 days as a pilot clinical observation.

Results: The combined iron chelator with anti-oxidant treatment ex-vivo showed significantly decreased ROS generation by 50% and decreased cell apoptosis.

Initial pilot results from the in vivo trial in 2 patients showed improved beta cell function, 10% decrease in HBA1C, improved results of platelet aggregation to ADP and Collagen, and slower optic nerve degeneration.

Conclusion: WFS2 is a severe progressive degenerative disease, lacking so for a specific pathophysiological based therapy. Based on the toxic effect of intra-mitochondrial iron accumulation in CISD2 mutations, Iron chelator therapy decreased iron accumulation, ROS formation and cell apoptosis in patients` cultured fibroblasts and improved metabolic parameters as well as platelet aggregation defects in the 2 first patients studied. In vivo and In vitro initial results are promising that the progression of WFS2 can be altered using this new treatment.

The adipokine FABP4 as a regulator of neonatal glucose homeostasis

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During normal pregnancy, fetal hepatic gluconeogenesis (GNG) is absent and is evident only soon after birth with a rapid increase in the expression of phosphoenolpyruvate carboxykinase (PEPCK). PEPCK expression is regulated by the adipokine fatty acid-binding protein 4 (FABP4 or aP2) which plays key roles in systemic metabolism and in promoting GNG. We hypothesized that FABP4 may play an important role in neonatal glucose homeostasis by regulating the GNG 'switch-on' immediately after birth. Therefore we studied the dynamics in serum levels of FABP4 from maternal, fetal and neonatal samples. Serum samples were collected from 47 pregnant women at term immediately before delivery (51% with gestational diabetes, GDM), from the umbilical artery and vein after birth and from the newborns within the first few hours of life. As previously described, women with GDM had significantly higher levels of FABP4 as compared to normoglycemic (24.7±15.9 vs. 15.2±7.6 ng/mL ng/mL, p=0.029). In the fetal circulation, FABP4 level was significantly higher than that observed in the non-diabetic maternal circulation (23.3±15.3 and 23.6±15.2 ng/mL for umbilical artery and vein, respectively vs. 15.2±7.6 ng/mL in normoglycemic women). Compared to fetal levels, the neonatal FABP4 levels after birth increased ~3-fold, reaching a value of 65.2±37.5 ng/mL (p0.001). In addition, neonatal FABP4 levels inversely correlated with blood glucose, reaching average level of 94.8±59.8 ng/mL among neonates who developed hypoglycemia (glucose 40 mg/dL). These increased FABP4 levels in hypoglycemic newborns were observed even in the presence of elevated insulin levels, known to suppress FABP4 secretion. Taken together, the significant increase in fetal FABP4 levels immediately before delivery, which continues to increase during the first hours of life coincides with the activation of GNG in the newborn. The rapid and robust increase in circulating FABP4 during hypoglycemia suggest that this adipokine can counter-regulate insulin action.

Natural History of Contralateral Nodules after Lobectomy in Patients with Papillary Thyroid Carcinoma

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Background: Bilateral thyroid nodularity in papillary thyroid carcinoma (PTC) patients is an indication for total thyroidectomy. However, the natural history and outcome of contralateral nodules after lobectomy has never been studied.

Objective: To investigate the natural history of non-suspicious contralateral nodules after lobectomy for PTC.

Methods: We included patients who underwent lobectomy for PTC, who had one or more nodules (size ≥3mm) in the contralateral lobe prior to surgery. The contralateral nodules were either benign on cytology, or were small and not suspicious per ultrasound.

Results: One hundred and eighteen patients were included in the study, operated between January 2002 and December 2013. The median age was 57 years (range 25-84), and the median size of PTC in the lobectomy specimen was 8mm (range 0.5-40). The median size of contralateral remaining nodules prior to surgery was 7mm (range 3-30). Thirty-four nodules (29%) were assessed by FNA prior to surgery, none was suspicious for malignancy. Over a median follow-up of 6 years, 29 nodules (25%) increased in size ≥3mm, with a median growth of 6mm (range 4-19). Twenty-two patients (19%) developed new nodules in the remaining lobe. Fifteen patients (13%) underwent completion thyroidectomy due to: growth of contralateral nodules (3 patients), suspected malignancy on FNA (9 patients with Bethesda groups III-V), or malignancy (3 patients). Overall, based on the completion thyroidectomy specimen, 8 patients (7%) were diagnosed with contralateral PTC (5 microPTC, one 20mm), of whom 7 underwent radioiodine ablation, and are all with no evidence of disease at the end of follow-up. There were no surgical difficulties or local complications related to completion surgery.

Conclusions: Lobectomy in patients with PTC and contralateral non-suspicious thyroid nodule/s is safe, but requires regular ultrasound follow-up as growth is seen in 25% of patients. In the few patients who required completion thyroidectomy, treatment with surgery and radioiodine is effective.

Iodine Insufficiency is Prevalent in Israel: Findings of a National Survey of School Age Children and Pregnant Women in the Maccabi Healthcare Services

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Introduction

National data on iodine status in Israel is lacking. Israel`s iodine-depleted water, the absence of a universal salt iodization (USI) program and reports of increased use of thyroid medication suggested that the population's iodine intake is likely inadequate.

Aims

To determine iodine status in the Israeli population in a nationally-representative sample of school age children (SAC) and pregnant women (PW).

Methods

Pre-discard spot-urine samples, from 1,023 SAC and 1,074 PW, representing all regions and major sectors in Israel (Arab, Jewish secular and orthodox) were collected during 2016 at the Maccabi Healthcare Services (MHS) central laboratory. Urinary iodine concentration (UIC) was measured using the modified Sandell-Kolthoff method, and analyzed by trimester, region and sector. The Ministry of Health and MHS ethical committees approved the research.

Results

The Israeli population is mildly deficient (SAC median UIC 83 μg/L; IQR 52-127) and PW are insufficient (median UIC 61μg/L; IQR 36-97), with 62% of SAC and 85% of PW below the World Health Organization's adequacy range (100-199 μg/L for the population as determined in SAC and 150-249 μg/L for PW). PW residing in Israel`s central district had significantly higher, though still insufficient, UIC (median 75 μg/L, n=256) than those residing in all other districts (p0.05); however, UIC did not differ by district for SAC.

Conclusions

The high prevalence of iodine insufficiency in Israel is a serious public health and clinical concern. A USI and monitoring program should be urgently initiated. Caregivers should recommend adequate iodine intake during pregnancy and lactation. A randomized clinical trial of risk and benefit for correction of mild-moderate iodine deficiency during pregnancy must be considered.

Long-term atherosclerotic cardiovascular and cerebrovascular morbidity in thyroid carcinoma patients: a retrospective cohort study

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***Background*:** An association between endogenous subclinical hyperthyroidism and increased cardiovascular morbidity has been shown in several studies. Iatrogenic subclinical hyperthyroidism is part of the standard treatment with levothyroxine in thyroid carcinoma (TC) patients.

***Aim*:** To assess atherosclerotic cardiovascular (CaV) and cerebrovascular (CeV) morbidity in TC patients (exposed, patient group) compared to individuals without any thyroid disease (unexposed group).

***Methods*:** This is a retrospective cohort study based on the database of Clalit Health Services. Follow-up started on January 1st, 2001 and ended on June 30th, 2016, with a mean of 7.7±4.2 years. The Cox regression hazard ratio (HR) and 95% confidence interval (CI) for atherosclerotic CaV&CeV morbidity in the exposed versus the non-exposed group was computed following adjustment for multiple cardiovascular risk factors.

***Results*:** 5,677 individuals aged 18 years and older, with TC and no history of other cancer were compared to 23,962 sex- and age-matched individuals with no thyroid disease. 154 (2.7%) in the patient group and 1,631 (6.8%) in the non-exposed group had prevalent atherosclerotic CaV&CeV diseases. During the study period, 555 (9.8%) and 1,856 (7.7%) new CaV&CeV events occurred in the respective groups. After adjusting for multiple cardiovascular risk factors, the risk of atherosclerotic CaV&CeV morbidity was increased in the exposed` group in total and following the exclusion of those with prevalent CaV&CeV disease (HR 1.26, 95% CI 1.15-1.39 and HR 1.23, 95% CI 1.12-1.36, respectively). Among exposed females, HR was increased in total as well as following the exclusion of prevalent CaV&CeV disease (HR 1.25, 95% CI 1.11-1.40 and 1.29, CI 1.14-1.46, recpectively). However, in exposed males increased risk was observed only in the total group (HR 1.20, 95% 1.01-1.42), but not for incident cardiovascular events.

***Conclusions*:** This large population study showed increased atherosclerotic CaV&CeV morbidity among TC patients compared to individuals without any thyroid diseases.

The Assaf Harofeh Medical Center Thyroid Cancer Registry: Clinico-pathological characteristics and disease outcome in 441 patients with non-medullary thyroid cancer.

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Background: The new ATA guidelines for management of thyroid nodules remain controversial and more clinical data is needed to support some recommendations. To this end hospital-based registries can be very helpful tools. We aim to stablish a database for all thyroid cancer patients treated at our institution.
Methods: Following approval of our institutional ethical board, a computer search using "thyroid neoplasm" as keyword was conducted for all hospital records during 1995-2015. Medical charts were reviewed and patients with proven diagnosis of thyroid carcinoma were included. Data on demographics, risk factors, medical history, diagnostic workup, primary treatment, follow-up and outcome were obtained and plotted in an excel spreadsheet. **Results***:* We retrospectively registered 441 non-medullary thyroid cancer patients treated at our institution during 1962-2015 (414 during 1990-2015), of whom 80% were operated either, in-house (65%) or privately (15%). Clinico-pathological characteristics were: mean age 47.7 years (over 45 yrs 59.7%), female 75.5%, familial 10.5%, radiation exposure 7.2%, PTC 89.1% (classical 63.3% follicular 25.8% variants), FTC 6.7%, others 4.2%. Disease extension at diagnosis was: microcarcinoma 33%, multifocality 38.3%, extrathyroid extension 20%, lymph node metastases 27.4%, distant metastases (DM) 4.7%, and TNM stage III-IV 25.7%. Near total thyroidectomy was performed in 86.6% and neck dissection in 25.7% patients. RAI was given to 86.5% patients, with a mean first dose of 110 mCi (10.3% received 30 mCi only). Additional treatment during follow up included reoperation in 8.5% and repeated RAI in 34.8%, for a median cumulative dose of 130 mCi (25% received more than 200 mCi). New DM were diagnosed in 5.8% patients. Persistent disease was recorded in 25% and 16% patients at 1 year and last visit, respectively. At a mean follow up of 9.7±8.8 yrs, the overall mortality was 10.4% and disease related mortality 3.1%.
Conclusions: This Israeli second-largest hospital-based thyroid cancer registry will add to bigger sample population in future clinical studies; it is dedicated to the memory of Phillip Hagag, who treated most of these patients

Hypothyroidism in pregnancy is associated with twin pregnancies and with adverse obstetric outcome: Analysis of 142,277 deliveries data from a single center

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Introduction:

Many studies have examined maternal and fetal complication rates in treated and untreated overt and subclinical hypothyroidism. Maternal hypothyroidism may adversely affect the development of the fetal pituitary-thyroid axis. It has also been reported to be closely related to adverse pregnancy outcome.

Aim:

To study the prevalence and outcome of hypothyroidism in pregnancy during the last decade in a high volume obstetric center in Jerusalem.

Methods:

A retrospective study of the obstetric database between August 2005 and December 2015 in Shaare Zedek Medical Center, Jerusalem.

Results:

During the study period there were 142,277 deliveries of singleton or twin pregnancies (1.9% twin deliveries). The medical files of 4042 (2.8%) deliveries (group A) included a diagnosis of maternal hypothyroidism. Women giving birth with the diagnosis of hypothyroidism were older (31.1±6 years 28.8±5.6 y. p0.0001). Gestational diabetes was more prevalent (7.3% vs. 3.3%, p0.0001) in group A as were hypertensive disorders (3.7% vs. 2.3%, p0.0001). Higher rate of pregnancies achieved by assisted reproduction techniques in group A (8.5% vs. 3.7%, p0.0001). Although not previously reported, the incidence of twin pregnancies was higher in group A (3.8% vs. 1.8% p0.0001) and this association remained significant in a multivariate analysis with IVF as a co-variate (OR 1.43 95%CI[1.20-1.71], p0.001). Obstetric complications including preterm deliveries (7.8% vs. 5.2%, p0.0001), cesarean sections (20.6% vs. 11.4%, p0.0001), any obstetric hemorrhage and prolonged hospitalization were more frequent in group A. The incidence of adverse neonatal outcome including low birth weight (7.3% vs. 5.4%, p0.0001) and NICU admission (5.1% vs. 3.6%, p0.0001) was higher in group A but there was no difference in fetal macrosomia and Apgar scores.

Conclusions:

In this large database, hypothyroidism is associated with adverse obstetric outcome. This is the first study to describe a higher incidence of hypothyroidism in twin pregnancies. TSH screening should be considered in twin pregnancies.

Risk factors for the development of delayed TSH elevation in Neonatal Intensive Care Unit (NICU) Newborns: Case Control Study

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Context: Delayed TSH elevation (dTSH) is defined as elevated TSH in the second neonatal screen (following normal TSH in the initial screen) in premature, low birth weight (BW) and sick newborns mostly in the setting of neonatal intensive care unit (NICU). The pathogenesis of dTSH is elusive

Objective: To identify risk factors for the development of dTSH among newborns in the NICU.

Design, setting and patients: A retrospective chart review of neonates with dTSH was conducted in eight university-affiliated NICUs. Two controls were selected for each patient, matched for gender and BW. Risk factors for dTSH were identified by univariate analysis followed by multivariate analysis.

Main outcome measures: Maternal variables, types of treatment and procedures in the NICU, syndromes, malformations and several clinical emergencies were compared between dTSH patients and their matched controls.

Results: 100 dTSH patients and 200 matched controls were enrolled and a comparison of 46 variables was conducted between the groups. 11 risk factors for dTSH were identified by univariate analysis: caesarian section, mechanical ventilation, patent ductus arteriosus (PDA) pneumothorax and the administration of cefotaxime, vancomycin, dopamine, ibuprofen, furosemide, insulin and packed cells. By multivariate analysis 4 risk factors were identified: PDA and vancomycin, insulin and furosemid administration. In 26 twin pairs where one twin had dTSH, all variables were similarly presented in both twins.

Conclusions: Although some variables have direct effects on the pituitary-thyroid axis dysfunction (dopamine, packed-cells), altogether these variables reflect the severity of the clinical conditions in the NICU, which is the common base for dTSH.

Trends in the Clinicopathological Features and Clinical Outcomes of Medullary Thyroid Carcinoma – An Israeli Multicenter Study

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Background: The massive use of neck sonography has led to a dramatic increase in the incidence of thyroid cancer detection, predominantly small papillary carcinomas. However, changes in the presentation and course of medullary thyroid carcinoma (MTC) over time remain unclear.

Objective: To evaluate trends in the presentation and outcomes of MTC.

Methods: Patients treated for MTC at four medical centers in Israel were divided into two groups by year of diagnosis, 1963-2005 (period A) and 2006–2016 (period B), and compared for clinicopathological variables.

Results: The cohort included 157 patients (52% female) of mean age 49.1±18.5 years (median 55.5) followed for 10.9±10 years. Eighty-six patients (54.8%) were diagnosed in period A, and 71 (45.2%) in period B. No significant between-group differences were found in primary tumor size at diagnosis (26.5±18.4mm and 24.2±19.4mm**,** respectively), proportion of micro-MTCs (<1cm) (14/62, 22.6% and 17/62, 27.4%, respectively), or TNM staging. Period A was characterized by a higher rate of familial MTC (25/83, 30.1% vs. 4/71, 6.8%; p=0.001) and lower age at diagnosis (45.6±18.9 years vs 54.6±16 years; p=0.003). Cervical lymph node dissection was more commonly performed in period B (43/64, 67.2% vs. 54/66, 81.8%; p=0.04). Nevertheless, this did not result in concomitant increase in the rate of metastatic lymph node excision (36/70, 51.4% and 37/63, 58.7%). There was no significant difference between groups A and B in disease-free survival at one year after diagnosis (32/70, 44.4% and 28/58, 48.3%, respectively) or disease-free state at last follow-up (26/72, 36.1% and 29/61, 47.5%, respectively, p=0.22).

Conclusions: Unlike differentiated thyroid cancer, most presenting features of MTC have not changed in recent years. The most significant temporal change is a decreased rate of familial MTC. Despite the use of more extensive surgical procedures and new treatment modalities, there has not been significant improvement in disease-related outcomes.

Sex Differences in the Impact Of Thinness, Overweight, Obesity and Parental Height on Adolescent Height

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Aim: The secular trend of increasing weight may lead to a decline in height gain compared to the genetic height potential. The impact of weight on height in healthy male and female adolescents compared to their genetic height was assessed. Methods: Height and weight were measured in Israeli adolescent military recrutees aged 16-19 years between 1967 through 2013. The study population comprised 355,229 recrutees for whom parental height measurements were documented. Subjects were classified into four BMI percentile groups according to the US CDC BMI percentiles for age and sex :<5th (underweight), 5th-49th (low-normal), 50th-84th (high-normal) and ≥85th (overweight-obese). Short stature was defined as height ≤3rd percentile and tall stature as height ≥90th percentile for age and sex.

Results: Overweight-obese females had a 73% increased risk for short stature (OR 1.73, 95%CI=1.51-1.97, p<0.001). Conversely, underweight females had a 56% lower risk of short stature (OR 0.44, 95%CI=0.28-0.70, p=0.001) and a two-fold increased risk for being tall (OR 2.08, 95%CI=1.86-2.32, p<0.001). Overweight-obese males had a 23% increased risk of being short (OR 1.23, 95%CI=1.10-1.37, p<0.001). Underweight females were on average 4.1 cm taller than their mid-parental height.

Conclusions: Overweight-obese males and females had an increased risk of being short compared to those with normal weight. A greater influence of body mass indesx (BMI) on height was observed in females. Underweight females were significantly taller compared to those with normal weight, and taller than their expected genetic height. The significantly increased height among underweight healthy females may reflect a potential loss of height gain in overweight-obese females

Peptide Receptor Radionuclide Therapy (PRRT) Efficacy in the Treatment of Functional and Metastatic Phaeochromocytoma (PCC) and Paraganglioma (PGL)

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Background: Treatment options for metastatic PCC/PGL and related hypertension (HTN) are limited. Experiences in PRRT suggest favourable disease control but lack of data on HTN response. We assessed PRRT outcomes in patients (pts) with high somatostatin receptor (SSTR) expression from 2 referral centres.

Methods: 15 pts (M:F = 11:4; 21-77 y.o) treated with ^{177}Lu-DOTA-octreotate (LuTate) were retrospectively reviewed. One pt was excluded due to unexpected death during PRRT. Median cumulative activity 21.5 GBq, most had 4 cycles (1-4 cycles), 7 had radiosensitising chemotherapy.11 pts were treated for functional HTN, and 3 pts for non-functional metastatic disease or recurrence.

Results: 6/11 pts (55%) had HTN improvement with reduction of anti-HTN medications at 3 months post PRRT, others (5/11) had HTN stabilisation without progression. 89% had serum chromogranin A reduction. For all pts cohort, 40% had disease regression (30% partial, 10% minor response) measurable on CT, and stable findings in 40%. Two pts had bony disease evaluable only on SSTR imaging (1 partial response, 1 stable disease). Two pts died, median overall survival not reached with median follow-up of 43.5months. The death during PRRT (post cycle 3) may be related to HTN crisis from inadequate alpha/beta blockade. Two pts had Grade3 lymphopenia, 1 Grade3 thrombocytopaenia, no significant renal toxicity.

Conclusions: In addition to favourable disease control and minimal toxicity from PRRT, our results also indicate potential clinical and biochemical effectiveness in pts with functional metastatic SSTR+ PCC/PGL. Adequate alpha/beta blockade is mandatory to prevent crisis. Prospective PRRT trials are warranted for this population with complex clinical and tumour heterogeneity.

The Effect of the Autophagy Inhibitor Chloroquine (CQ), Alone or in Combination with mTOR Inhibitors, on Neuroendocrine Tumor (NET) Growth & Metastatic Spread in Mouse Models

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Background: mTOR inhibitors (mTORi) such as RAD001 demonstrated promising anti-cancer effect in NETs. Autophagy, a cell survival mechanism, is activated by mTORi. We have recently shown in the human NET cell line BON1 that autophagy is essential for cell survival. Treatment with CQ alone or together with mTORi robustly inhibited cell proliferation and survival, suggesting that treatment with CQ may potentiate the anti-tumorigenic effects of mTORi.

Aim: To examine the possible anti-proliferative effects of these drugs in three *in vivo* NET mouse models.

Methods: We utilize three mice *ex vivo* models: BON1 subcutaneous xenografts, BON1 liver metastasis, and a human NET subcutaneous transplantation.

Results: In the BON1 xenograft mice model, CQ alone but mainly in combination with RAD001 significantly decreased the average tumor volume ($620mm^3$ and $113mm^3$, respectively). Histopathological analysis revealed that CQ caused an increase in tumor LC3 levels (an autophagy marker) while in combination with RAD001 the increase in LC3 was even more marked (mean fluorecense intensity (MFI) of 6.7 and 14.5 respectively), suggesting inhibition of autophagy in these tumors. CQ induced tumor cell apoptosis (by TUNEL analysis), both alone and mainly in combination with RAD001 (MFI of 5.5 and 8.2 respectively).

Conclusions: These preliminary results suggest a favourable effect for chloroquine, alone and mainly in combination with mTORi, in suppressing NET growth in the BON1 subcutaneous xenograft model by inducing apoptosis. Further studies are needed to confirm the possible additive effect of these drugs in overcoming mTORi-associated drug-resistance, and before considering their use in clinical trials in patients with refractory NETs.

The Tumor Tuppressor Klotho: A Master Regulator of Metabolism in Breast Cancer

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Background: One of the hallmarks of cancer is reprogramming of energy metabolism, characterized by a shift to aerobic glycolysis (Warburg effect). The metabolic shift is regulated by many factors, among them the growth factor insulin-like growth factor (IGF)-1. Another regulator of energy metabolism is the energy sensor enzyme, AMP-activated kinase (AMPK) which is activated by the tumor suppressor liver kinase-B1 (LKB1) and elevated AMP/ATP ratio. Klotho is a trans-membrane protein, which can be cleaved and act as a hormone. We showed that klotho inhibits the IGF-1/PI3K/AKT pathway in pancreatic and breast cancer (BC) and identified it as a tumor suppressor in these malignancies.

Aim: To study whether klotho interferes with BC cells metabolism thus leading to reduced cell survival.

Methods: Experiments were conducted in MCF-7, T47D and MDA-MB-231 BC cells. Proliferation and cell migration were tested using colony formation and wound healing assays. Signaling pathways were determined using Western Blotting. Gene expression was analyzed using qRT-PCR. Mass spectrometry and NMR were conducted to measure metabolites levels. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured using Seahorse technology. Mitochondrial membrane potential was studied by flow cytometry of DioC6

Results: Klotho inhibited glycolysis, as evidenced by reduction of EACR, glucose uptake, lactate production and expression of key glycolytic enzymes. Interestingly, klotho also inhibited mitochondrial activity as it reduced mitochondrial membrane potential, OCR and ATP production. Elevated AMP/ATP activates AMPK, indeed, klotho increased AMPK phosphorylation, whereas a dominant negative LKB1 prevented this activation. Furthermore, it decreased the ability of klotho to inhibit cell proliferation and migration, implying klotho tumor suppressor activity is AMPK/LKB1 dependent.

Conclusions: Our data indicate klotho, for the first time, as a regulator of metabolic activity in breast cancer and suggest that reversal of the metabolic switch is a key mechanism of klotho`s tumor suppressor activity.

Estrogen receptor activating mutations confer an aggressive phenotype to endocrine resistance breast cancer cells through alteration of tumor metabolism

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Background: Although endocrine therapy is successfully used to treat patients with estrogen receptor (ER) positive metastatic breast cancer, all these patients will eventually relapse. Several mechanisms of acquired resistance have been described, amongst them, activation of mTOR. Recently we and others identified novel mutations in the ligand binding domain (LBD) of the ER which confer constitutive transcriptional activity and resistance to endocrine therapies. Clinical data suggest more aggressive characteristics of tumors expressing these LBD-mutations.

Aim: We aimed to elucidate whether LBD-mutations confer a more aggressive phenotype compared to wild-type (WT)-ER, assess the interaction of LBD-mutations with the mTOR pathway and to discover novel strategies to inhibit the activity of the mutated receptors.

Methods: MCF-7 cells expressing physiological levels of LBD-mutations were generated using CRISPR/Cas9. Proliferation, migration and tumorigenicity were tested using MTT, wound healing and soft agar assays. Gene-expression analysis was performed using affimetrix®, qRT-PCR and western blotting. Cellular metabolism was studied by monitoring oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) using Seahorse technology.

Results: Cells expressing LBD-mutations exhibited higher proliferation, migration and tumorigenicity, even in the presence of estrogen, compared to WT-ER cells, indicating increased aggressive phenotype. Gene expression analysis revealed upregulation of genes involved in invasion and metastases in LBD-mutation cells. Both OCR and ECAR were elevated in cells expressing activating mutations, indicating increased glycolytic and mitochondrial activities. While inhibition of mTORC1 using rapamycin inhibited only WT-ER cells, dual inhibition of mTORC1 and mTORC2 overcame the resistance of the mutated receptor, abolished its constitutive transcriptional activity and abrogated enhanced aggressive phenotype.

Conclusions: Our study indicates that the mutated receptors confer a more aggressive phenotype and a higher metabolic rate to breast cancer cells and suggest a novel treatment strategy- dual inhibition of mTORC1 and mTORC2.

Pegvisomant for acromegaly: a cohort of 36 Israeli patients

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Introduction: Somatostatin analogs are the first-line treatment for acromegaly, whereas the GH-receptor antagonist, pegvisomant, is given to patients who remain inadequately controlled. Pegvisomant is reimbursed in Israel since 2008.
Aim & Methods: We have identified in two referral pituitary centers 36 patients (21 males) with acromegaly treated with pegvisomant, either alone or in combination with somatostatin analogs, and characterized their clinical characteristics and response to treatment.
Results: Mean age at diagnosis was 35.8+11 years (range, 16-62 years). The cohort included 25 subjects with macroadenomas, 6 giant adenomas (40 mm), and 5 microadenomas. Twelve patients had visual fields damage. Mean baseline IGF-1 was 3.2+1.3 X upper limit of normal (ULN). All patients besides three underwent pituitary surgery, but none achieved hormonal remission following surgery. Ten patients underwent sellar radiotherapy. All patients were initially treated with somatostatin analogs before starting pegvisomant (octreotide LAR, 30; lanreotide, 6). Under somatostatin analog treatment, mean IGF-1 was 2.2+0.7 X ULN. Subsequently, 17 patients were switched to pegvisomant monotherapy, whereas 19 received combination therapy with a somatostatin analog. Daily pegvisomant dose was 5 mg (n=1), 10 mg (n=8), 15 mg (n=6), 20 mg (n=10), and 30 mg (n=11). After a mean treatment interval of 56 months mean IGF-1 levels were 0.98+0.6 X ULN. Fourteen subjects on pegvisomant monotherapy achieved hormonal remission and two were uncontrolled (one died before assessment); in the combination group – 13 were in remission and 6 remained uncontrolled. Altogether, 27 out of 35 patients (77%) treated with pegvisomant normalized IGF-1, and another 3 suppressed IGF-1 to below 1.2 X ULN. Among the 12 patients with IGF-1 2.5 X ULN before treatment with pegvisomant, 8 (67%) normalized IGF-1.
Conclusions: In the real-life scenario three-quarters of patients with acromegaly, resistant to somatostatin analogs, are expected to respond to pegvisomant, given either alone or in combination with octreotide/lanreotide

The role of the nucleolar protein PICT-1 in the tumorigenesis of neuroendocrine tumors and its interaction with the p53 pathway

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Background- PICT- 1 is a nucleolar protein which has been revealed as a key regulator of cell fate and nucleolar stress response. PICT-1 was suggested to act as a tumor suppressor which interacts with PTEN or controversially as an oncogene which causes the inhibition of p53.

Aims- The goal of this study was to identify the role of PICT-1 in the development of neuroendocrine tumors (NETs) and to decipher its mechanism of action.

Study Model- We utilized human cell lines of lung (NCI-727), medullary thyroid (TT) and pancreatic (BON1) NETs which exhibit divergent status of p53, making their use ideal for this study. We also used tissues of a variety of NET patients for PICT-1 immunohistochemistry analysis.

Results- PICT-1 overexpression induced a significant increase in cell viability of NCI-H727 and TT cells. Strikingly, it also induced the appearance of a low molecular weight p53 which lacks the C-terminus end. A robust decrease in p21 expression was found suggesting that the shortage of p53 caused its inactivation. Proteasomal degradation, cleavage by caspase and alternative splicing were tested and neither of these mechanisms was found to cause p53 shortage. Direct interaction of PICT-1 and p53 was also ruled out. As mTORC1 is known to affect nucleolar functions and moreover, its inhibitor, everolimus (RAD001), was found useful to inhibit pancreatic NET, we undertook to examine if PICT-1 may function as a sensor or effector of RAD001 in NETs. PICT-1 overexpression completely reversed the RAD001- induced reduction in cell viability of TT cells. Immunohistochemistry studies in human bronchial NETs show cytoplasmatic localization of PICT-1 in the normal bronchus whereas bronchial NETs show also nuclear staining with higher intensity.

Conclusions- Our study suggests that PICT-1 may have an oncogenic function in NET cells through modulation of the p53 pathway. Moreover PICT-1 is a potential prognostic marker of the efficacy of mTOR inhibitors.

Plenary lecture 3:

Autoimmune Thyroid Diseases: From Gene Mapping to Novel Drug Targets

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Autoimmune thyroid diseases (AITD) including Graves' disease (GD) and Hashimoto's thyroiditis (HT) are characterized by breakdown of tolerance to thyroid antigens leading to infiltration of the thyroid by autoreactive T-cells, and production of autoantibodies targeting the thyroid gland. AITD are believed to result from an epigenetic interaction between susceptibility genes and environmental triggers. AITD susceptibility genes can be broadly categorized as either thyroid specific (Tg, TSHR) or immune-modulating (HLA-DR, CTLA-4, PTPN22, CD40, FOXP3, CD25). Most of the genes predisposing to AITD participate in the immunological synapse which is the interface between antigen presenting cells and T cells created during antigen presentation. Among the immunological synapse genes HLA-DR containing arginine at position 74 of the beta chain gives the strongest risk. Understanding the importance of the immunological synapse in the etiology of AITD has paved the way to blocking antigen presentation as a novel therapeutic approach to AITD. Indeed, new therapeutic approaches targeting the immunological synapse are being developed. Dissecting the mechanisms leading to AITD will hopefully lead to future antigen-specific precision therapies.

Symposium 6: Cellular Heterogeneity

Cellular heterogeneity in the liver: from single RNA molecule organization to organ function

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The mammalian liver consists of hexagon-shaped lobules that are radially polarized by blood flow and morphogens. Key liver genes have been shown to be differentially expressed along the lobule axis, a phenomenon termed zonation, but a detailed genome-wide reconstruction of this spatial division of labour has not been achieved. To this end we measured the entire transcriptome of thousands of mouse liver cells and infered their lobule coordinates on the basis of a panel of zonated landmark genes, characterized with single-molecule fluorescence *in situ* hybridization. Using this approach, we obtained the zonation profiles of all liver genes with high spatial resolution. We found that around 50% of liver genes are significantly zonated and uncovered abundant non-monotonic profiles that peak at the mid-lobule layers. These included a spatial order of bile acid biosynthesis enzymes that matches their position in the enzymatic cascade. Our approach can facilitate the reconstruction of similar spatial genomic blueprints for other mammalian organs.

Does ketoacidosis at onset of type 1 diabetes is a predictor of long-term metabolic control?

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Background: Only few studies evaluated the impact of diabetic ketoacidosis (DKA) at diabetes onset on the long-term metabolic control in patients with type 1 diabetes (T1D).

Aim: To evaluate if there are differences in the long-term metabolic control between children/adolescents with T1D who presented with DKA at diabetes onset and those who were diagnosed without DKA.

Methods: retrospective study based on files data of patients diagnosed with T1D from 1/2007-12/2012, and followed at the National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel.

Inclusion criteria were: patients18 years at diabetes onset, diabetes duration≤2 years and regular clinical follow-up at the diabetes clinic.

Variables compared between patients with DKA and those without DKA at onset included: yearly HbA1c levels, daily insulin dose, rates of yearly severe hypoglycemic episodes and DKA events, and the percent of patients that achieved the target HbA1c levels.

Results: The study population comprised 335 patients; of them 132 (39.4%) presented with DKA. After the first year of diabetes, the mean daily insulin dose and HbA1c level were significantly higher in the group with DKA at onset vs. the other group (0.74±0.26 vs. 0.69±0.27 units/kg/day, p=0.049, and 7.85±1.13% vs. 7.49±0.94%, p=0.01, respectively), despite similar mode of therapy in both groups.

During the entire diabetes duration, the group without DKA at onset vs. the group with DKA had a significantly lower mean HbA1c (7.86±0.95% vs. 8.08±0.95%, p=0.025), had a significantly higher percentage of patients that achieved HbA1c levels within the glycemic targets (32% vs. 20.5%, p=0.02), and a significantly lower frequency of DKA episodes per diabetes years (p=0.042).

Conclusions: DKA at diagnosis was associated with less favorable long-term metabolic control as assessed by HbA1c and the rate of DKA episodes. Therefore, patients with T1D diagnosed with DKA may need stricter treatment and tight follow-up from the early stages of the disease.

The real-life appearance of ketoacidosis in T2DM patients treated with SGLT2 inhibitors

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Introduction: SGLT2 inhibitors (SGLT2i) are a relatively novel class of antidiabetic medications. Latest studies have shown their ability to reduce body weight, cardiovascular morbidity and mortality. However, the results of several studies seem to contradict these outcomes, pointing out a likelihood of serious side effects, such as renal impairment, ketoacidosis (KA), urinary tract infections, increased fracture risk, and even toe amputations. Still, the causes and real frequency of "*euglycemic*" KA remain as vague as the term itself. All of the above urgently requires real-practice data, which may shed some light on these not fully understood effects.

Objectives: To investigate the frequency of KA occurrence and to evaluate possible risk factors of its development.

Methods: We performed a retrospective analysis of medical records of all 136 type 2 diabetes mellitus (T2DM) patients treated in our institute with SGLT2i and Metformin combined with incretin-based therapy (Mt-IBT) . Patients starting SGLT2i treatment in our institute, receive a kit to measure β-hydroxybutirate concentration in capillary blood (Free Style Optium). With this kind of approach three cases of KA, proved by elevated capillary β-hydroxybutirate concentrations were found.

Results: Rapid improvement in glycemic control with subsequent insulin withdrawal was discovered in all three cases. In two patients, recent hospitalization and food intake restriction were also noted. All three cases were characterized by intensive weight loss resulting from the negative calorie balance induced by SGLT2i. In parallel, a CGM-proved hypoglycemia was found in other nine patients on SGLT2i. We suggest *prolonged hypoinsulinemic hypoglycemia* to be the main pathophysiological mechanism of KA development.

Conclusions: Rates of KA and hypoglycemia were revealed to be more frequent than previously reported. Pathophysiological link between the two conditions is assumed.

The incidence of type 1 diabetes is increasing faster in familial than in sporadic cases.

Eighteen years of the Israeli Pediatric Diabetes Registry

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Objective

The global rise in the incidence of type 1 diabetes (T1D) is too rapid to be attributed to susceptible genetic background, which emphasizes a significant role for environmental factors. Unlike the theory that the need for genetic susceptibility has lessened over time, we hypothesized that the incidence rise of T1D is faster in genetically susceptible population.

Research design and methods

The study population comprised of 5077 T1D patients aged 0-17 years who were reported to the National Israel Diabetes Registry between 1997-2014. The patients were divided into familial cases where a first degree relative has T1D, and sporadic cases. Demographic and clinical data were retrieved from the registry. Annual incidence rates were computed separately for the sporadic and familial cohorts.

Results

The familial cases (n=583; 11.5%) and the sporadic cases (n=4494; 88.5%) were comparable for gender and seasonality of T1D onset. The proportions of non-Jewish ethnicity and very young age at diagnosis (0-4 years) tended to be higher in the familial *vs.* sporadic group (p=0.07 for both). Diabetic ketoacidosis was twice as common in the sporadic *vs.* familial cases (*p*0.0001). Consanguinity was more common in the familial than the sporadic group (10% *vs.* 6.1%; p=0.0007), especially among Jews. The rate of T1D annual incidence in the familial cases increased at a faster pace than the rate in the sporadic cases: 4.78% vs. 2.73% (p=0.018 by the generalized linear regression model).

Conclusions

The fast rise in T1D incidence in familial cases suggests that environmental factors impose a higher diabetogenic pressure in patients with a susceptible genetic background.

The relations between different risk factors for type 2 diabetes mellitus and glucose levels in people without diabetes in different sectors in the north of Israel

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Background: The prevalence of type 2 diabetes mellitus is increasing in Israel. This study investigated risk factors related to high glucose level in people without diabetes in northern Israel.

Methods: This study is a collaboration between Galilee Medical Center and The Israel Diabetes Association (IDA). IDA volunteers offered blood glucose measurement to visitors in Galilee Medical Center. After blood glucose level was measured by glucometer, the examinees were invited to complete an anonymous questionnaire. People with known diabetes, age less than 18 years old, acute disease and glucocorticoids usage were not included.

Result: 637 participants, 335 male, average age 48.9±15 years were included. The average blood glucose level, less than 4 hours after meal was 107.5±21.85 mg/dl (n=487) and more than 4 hours after meal was 98.25±13.49 mg/dl (n=126) a significant difference (t=5.94, p0.01). There was no significant difference between the religious sectors (p-value=0.666 ANOVA) and the levels of religiosity (p-value=0.616 ANOVA). Education level was associated with little but significant relationship to blood glucose level 107.8±22.9 mg/dl (less than 12 school years) versus 102.3±17.4 mg/dl (more than 12 school years) (t=5.94, p0.01). There was no relationship between diabetes in the family, physical activity, eating habits and sleeping habits and glucose level. Higher glucose levels were found in participants who thought of themselves as unhealthy (t=2.27, p-value0.026) or stressed (t=2.21, p-value0.028(

Conclusion: Quality of life indices were associated with higher blood glucose in people without diabetes in northern Israel.

The Effect of Admission on Glycemic Control in Elderly Patients with Diabetes Mellitus

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BACKGROUND AND OBJECTIVE: Diabetes mellitus (DM) has been shown to increase hospital admission rates by 2-6 fold compared to the general population. Previous studies have proven HbA1c is an independent risk factor for recurrent hospitalizations. However, the influence of hospitalization on glycemic control has not been reported. Our aim was to assess admission effects on HbA1C levels. We also investigated the short- and long-term mortality risk following hospitalization in patients with DM, according to HbA1c levels prior to the index admission.

METHODS: Five thousand medical records of ≥65 year old patients with type II DM, hospitalized between 2011 and 2014 in medical wards of Rabin Medical Center were screened. HbA1c levels before and after admission were documented. Demographic, clinical and biochemical data were recorded, including DM duration and recurrent hospitalizations. Total follow up time was up to 6 years.

Results: The final cohort included 2,000 patients. The average age was 77y, and 76% had DM for 10 years or more. Patients were classified according to HbA1c levels before hospitalization as follows: 6.5%, 6.5-6.9%, 7-7.9%, 8-8.9%, 9%. Comparing HbA1c before and after hospitalization has shown a significant reduction in HbA1c levels in the groups of patients with HbA1c levels between 8-8.9% and 9%. On the other hand, there was a slight increase in HbA1c levels in those with pre-admission HbA1c lower than 6.5% and between 6.5-6.9%. A competing risk analysis proved a significant increase in risk for recurrent hospitalizations among patients with HbA1c above 9% (p0.01). Hospitalization rate in patients with HbA1c 9% was higher compared to patients with HbA1c between 6.5-6.9% (4 vs. 3, p0.01). There was no association between in-hospital mortality and pre-admission HbA1c levels. Mortality at end of follow up was greater in patients with HbA1c9% (43%) and 6.5% groups (42%), compared to HbA1c 6.5-6.9 (34% (p0.01)

Conclusions: Unbalanced HbA1c prior hospitalization has been associated with increased hospitalization rate and increased mortality. Hospitalization has a beneficial effect on HbA1c levels in patients with HbA1c above 8%.

Admission Blood Glucose and Long Term (10-year) Mortality among Patients with or without Pre-existing Diabetes Mellitus Hospitalized with Heart Failure

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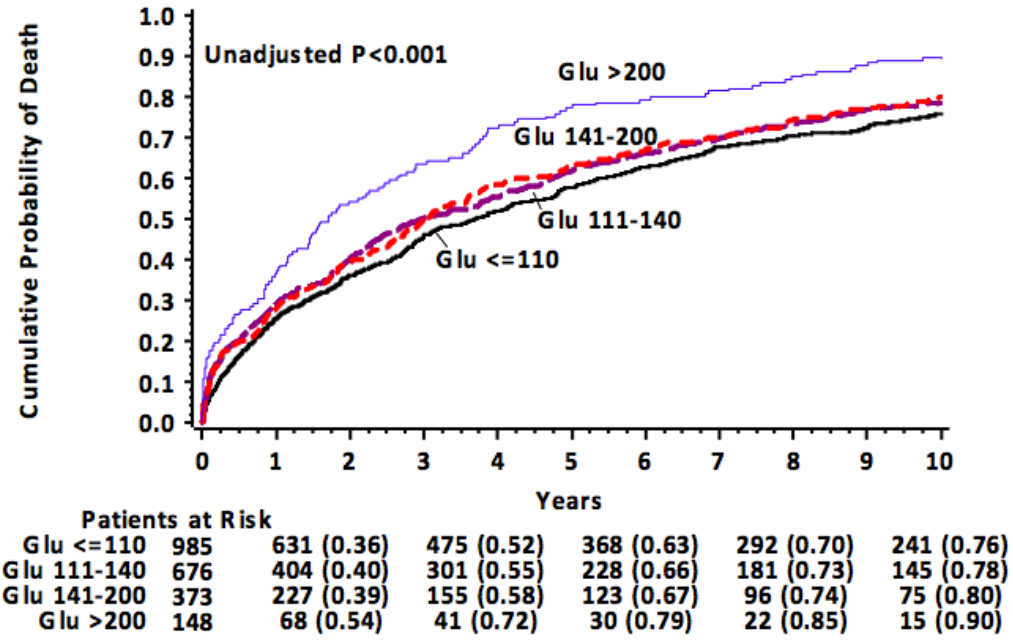
Aims: High admission blood glucose (ABG) level has been associated with a poor short-term outcome among non-diabetic patients with heart failure (HF). The present study was designed to investigate the association between ABG levels and long-term (10 years) mortality in patients with or without pre-existing diabetes mellitus (DM) admitted with HF.

Methods and results: We analyzed data on 1,811 patients with DM and 2,182 patients with no pre-existing DM who were hospitalized with HF during a prospective national survey. The relationship between ABG and 10-year mortality was assessed using the Cox proportional hazard model adjusting for multiple variables. ABG was analyzed both as a categorical (110, 110-140, 140-200, and 200 mg/dL) and as a continuous variable.

At 10 years of follow-up the cumulative probability of mortality was 85% and 78% among patients with DM and patients with no pre-existing DM (p0.001), respectively. Among patients with no pre-existing DM, glucose levels of 110-140, 140-200 and ≥200mg/dL were associated with 9% (p=0.140), 16% (p=0.031) and 53% (p0.001) increased mortality risk compared to ABG110 mg/dL. Each 18-mg/dL (1-mmol/L) increase in glucose level was associated with a 5% increased risk of mortality (p0.001) among patients with no pre-existing DM. In contrast, among patients with DM, only those with glucose levels 200mg/dL had an increased mortality risk (200mg/dL versus 110 mg/dL; HR=1.20, p=0.032).

Conclusion: Among hospitalized HF patients with no pre-existing DM there is a linear relationship between ABG level and long-term mortality, whereas among patients with DM only ABG level 200 mg/dl is associated with increased mortality risk.



The challenge of successful aging with diabetes- a novel clinical approach: integrating cognitive & physical assessment into the evaluation process

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Older people with diabetes are at greater risk for cognitive and physical impairment and these may present barriers to self-care ability. We introduce a novel approach assimilating cognitive and physical assessment into the multi-disciplinary evaluation. The service fosters a personalized intervention based on the following 5 components: 1) Staff a neuropsychologist, physiotherapist and occupational therapist participate in the multi-disciplinary team in addition to a physician, nurse and dietitian; 2) Evaluation: cognitive, emotional, physical (aerobic, strength and balance) and functional assessments are integrated into the multi-disciplinary evaluation; 3) Tailor made recommendations and a follow up plan that takes into consideration the cognitive, physical functional and emotional profile of the older individual (including cognitive rehabilitation strategies); 4) Repeated measurement: Following the initial evaluation each participant is invited periodically according to age and risk for decline to follow-up evaluations. Thus, creating a personalized individual cognitive/physical/functional slope and enabling early detection of fast decliners; 5) Infra-structure: One assessment day is scheduled for each individual in which he/she is examined by all specialists in one location thus eliminating the need to schedule and commute to multiple appointments. The feed-back session is conducted on a different day in order to prevent fatigue and improve comprehension. Data regarding the first 119 individuals over the age of 60 with type 2 diabetes who were referred because of difficulties in managing their disease was analyzed. 19 (16%) of individuals were deemed to meet the criteria for severe cognitive impairment, 50(42%) for mild cognitive impairment, 4(3%) met the criteria for severe physical disability and 25 (21%) for mild physical disability. The data collected demonstrates that a substantial proportion of the individuals referred are at high risk for disability (dementia, cognitive impairment, frailty) and highlights the importance of adding age-related parameters to the multidisciplinary evaluation of the older person with diabetes.

Do adding B vitamins and folate to metformin treatment has

beneficial effect on renal function and HDL cholesterol in patients with type 2 diabetes?

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Introduction Metformin is effective in reducing cardiovascular mortality, however may decrease vitamin B12 and folate levels, and increase levels of homocysteine. Hyperhomocysteinemia is associated with adverse impact on lipid parameters and renal function. The present study was designed to determine the effect of homocysteine lowering therapy by using group B vitamins and folate supplementations on lipid metabolism especially HDL cholesterol as well as kidney function assessed by serum creatinine, urine microalbumin (MA), albumin creatinin ratio (MaCR) and GFR in diabetic patients treated with high doses of metformin.

Methods In a randomized, placebo-controlled study, 60 diabetic patients treated with a high dose of metformin were randomly assigned to receive daily oral supplementation with folate (1000 mcg), vitamins B12 (400mcg) and B6 (10 mg) (Group 1) or placebo (Group 2). Metabolic parameters were measured at baseline and after 4 months folow-up.

Results The two groups were similar at baseline in terms of metabolic parameters. After 4-months, HDL cholesterol was significantly greater in patients who received vitamin supplementation than patients in the placebo group (p0.0001). Post-treatment vitamin B12 and folic acid levels were greater in group 1 vs. group 2 (p=0.007 and p0.0001, respectively). Hcy level decreased significantly in the treatment group from 10.0+/-4.4 to 7.6+/-2.5 mol/l, p=0.002 and did not change in the placebo group (p=0.964). In GLM model, group was significant independent predictor of endpoint HDL choleserol (p=0.018), while post-treatment LDL cholesterol did not differ by group after controlling for the other variables in the model (p=0.158). Posttreatment GFR was significantly greater in patients who received vitamin supplementation than patients in the placebo group (p0.003). Plasma creatinine, urine protein and urine microalbumin did not differ significantly by treatment group at baseline at the end of the study. Nevertheless, within the vitamin -treated group, MaCR dcreased from baseline (p0.036) and did not change in the placebo group.

Conclusion Adding B vitamins and folate supplementations to metformin was associated with beneficial effects on HDL cholesterol and renal function in diabetic patients.

Carotid IMT and Plasma Lipid Levels Among Children and Adolescents With Familial Hypercholesterolemia. A Single Center Experience 2007-2014

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Background: Familial hypercholesterolemia (FH) is an inherited error of lipoprotein metabolism characterized by elevated cholesterol and premature atherosclerotic cardiovascular disease. Current guidelines advocate early evaluation in pediatric carriers of FH. Assessment of carotid intima media thickness (cIMT) is often used to evaluate preclinical atherosclerosis in FH. Early cIMT progression was observed in FH subjects, and statin therapy was shown to slow the progression of IMT.

Aim: The objective of study was to determine the relation between plasma cholesterol levels, age and cIMT in young patients with FH.

Methods: Plasma lipid profile testing and cIMT measurements were performed on a group of FH patients which consisted of children and adolescents with a clinical and biochemical diagnosis of FH , from the pediatric lipid clinic at the Sheba medical center. The control group for the cIMT measurements consisted of fifty five (33 females) healthy normocholesterolemic subjects aged 18-30 years.

Results: 37 patients were assessed, 18 males and 19 females. The average age at assessment was 12.1±3.2 years for the males and 11.6±3.5 for the females.

Fasting plasma LDL-cholesterol levels were (mg/dl) 210.2±62.3 for the females and 198.7 ± 45.2 for the males.

Average cIMT values in males were 0.5±0.05 mm and 0.46±0.06 mm in females, and 0.488±0.05 mm in the control group. 11 males over the age of twelve years, had cIMT values above the control group.

Conclusions: cIMT was linearly related to age in both genders and is increased in male FH adolescents. Particular attention should be payed to this high risk group of patients.

Gestational diabetes risk in three Israeli population subgroups

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Objective: Israeli Ethiopian Jews (EJ) and Arabs have at reproduction age higher incidence of diabetes than other Israeli Jews. We aimed to compare gestational diabetes (GDM) risk among these population subgroups.

Methods: The study cohort included age-matched EJ, non-Ethiopian Jews (NEJ) and Arab women age 20 to 45 years. GDM diagnosis was based on the 2 step screening method of 50 grams and 100 grams oral glucose load tests. Univariate comparisons and the association between population subgroups and the risk for GDM were tested in multiple logistic regression analysis, adjusted for age, parity and pre-gestational levels of the metabolic syndrome components.

Results: The study included 13,943 women (2,938 EJ, 5,156 NEJ and 5,849 Arabs). During the years 2008-2011, birth rate was 0.358, 0.475 and 0.526 [p0.001], diabetes screening was performed in 84%, 81%, 85% and GDM prevalence was 4.3% 2.2% and 2.9% among Ethiopian, non-Ethiopian and Arab women respectively. The multivariate odds ratios (OR) for GDM were age 2.9-per 10 years (95% CI 2.1-4.1), BMI 1.12 (95% CI 1.1- 1.2), triglycerides 1.05-per 10mg/ml (95% CI 1.0- 1.1), systolic blood pressure 1.05-per 10mmHg (95% CI 1.02- 1.1), parity 0.8 (95% CI 0.7-0.9) and Ethiopian ethnicity 2.55 (95% CI 1.6-4.1). Arab-ethnicity 1.4 (95% CI 0.95-2.15) and HDL-c 0.99 (95% CI 0.91-1.08) were not associated with risk for GDM.

Conclusions: Ethiopian ethnicity is an independent risk for GDM. The higher GDM prevalence in Arab women is mainly explained by higher obesity rates.

Placental maternal and fetal vascular circulation in healthy non obese and metabolically healthy obese pregnant women. Metabolically healthy obese, but are they really?

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Background: Obesity in pregnancy is associated with hyperinsulinemia, impaired endothelial function, inflammatory up-regulation and higher risk of placental pathological lesions. However not all obese individuals demonstrate similar metabolic profiles. The present study was designed to investigate placental histopathology in lesions that are associated with maternal and fetal circulation abnormalities, in nonobese and obese women with and without metabolic alterations.

Methods: 332 pregnant women were divided into three groups according to presence of obesity and metabolic risk factors: Group 1 included 163 non-obese metabolically normal (NOMN); Group 2 included 106 obese metabolically normal (OMN); Group 3 consisted 63 obese metabolically abnormal (OMA) subjects.

Results: Placental weight was significantly higher in OMN compared to NOMN (p0.000). Maternal vascular supply (MVS) abnormalities of the placental bed differed significantly across groups, and increased from Group 1 to Group 3 in a continuous fashion (31%,38% and 54% respectively, p0.005). Fetal vascular supply (FVS) abnormalities rate increased from group 1 to group 3, and was significantly higher in obese subjects with and without metabolic abnormalities, compared to non-obese subjects (9%, 20% and 22% respectively , p0.021). Willus maturation defect (WMD)rate was higher in OMN subjects compared to NOMN (p0.018). In the logistic regression analysis, obesity emerged as a significant predictor of fetal vascular supply abnormalities (p=0.001) and WMD (p=0.011).

Conclusion: We demonstrated that obesity, per se, is associated with an increased rate of fetal vascular malperfusion abnormalities, Willus maturation defect, as well as higher placental weight and lower FPR, compared to non-obese subjects.

Does a first-degree family history of diabetes impact placental vascular circulation, inflammatory placental lesions, and pregnancy outcome?

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OBJECTIVE Heritability of diabetes is associated with hyperinsulinemia, impaired endothelial function and inflammatory up-regulation. However, no studies have examined whether a family history of diabetes effects placental vascular circulation.The present study was designed to investigate the impact of first-degree family history of diabetes (FHD) on placental vascular circulation , inflammatory lesions, and pregnancy outcome.

RESEARCH DESIGN AND METHODS 339 pregnant women were divided into two groups according to presence of first-degree FHD: Group 1 included 255 subjects without FHD, and group 2 included 145 subjects with FHD. Placental histology was performed for vascular circulation, as well as inflammatory lesions of maternal and fetal origin. Maternal and neonatal outcome parameters were collected.

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

CONCLUSIONS: FHD is associated with an increased rate of MVS abnormalities and adverse pregnancy outcome.

High serum estradiol defines a sub-phenotype of the metabolic syndrome (MS) in men and may protect from the metabolic and vascular sequels of obesity

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Obese men have lower serum testosterone (T) due to lower sex-hormone-binding-globulin and hypothalamic-pituitary-suppression by high, excess fat cell aromatase-derived estradiol (E2). Because T up regulates muscle mass whereas T and E2 exert distinct and complex effects on body fat and fat distribution we reasoned that variation in testosterone/estradiol status may be linked to distinct phenotypes in the MS in men. In 58 men and 70 women with MS (ATPIII) bioavailable T (BT) and E2 were divided arbitrarily to "low" or "high" by their median respective levels, corresponding to 41pg/ml for E2 and 1ng/ml for BT. The high E2 group (HE2; n=27) was similar to the low E2 group (LE2; n=31) in terms of age (50.1 vs. 52.7 yrs; p=NS), but had a higher BMI (36.6 vs. 33.0kg/m2; P0.0025), larger waist circumference (WC; 121 vs. 112.2 cm; P0.005), higher fat mass (38.9 vs. 34.2% DEXA, GE; P 0.0003) and a lower lean mass-fraction (61.1 vs. 65.8%; P0.0003). However, neither the serum lipids nor HbA1c were higher in the HE2 compared to the LE2 group. Likewise, 24 ambulatory-blood-pressure-monitoring, large artery rigidity as measured by carotid-femoral-pulse-wave-velocity (PWV) and endothelial function measured by flow-mediated-dilation (FMD) at the brachial artery were not different between high/low E2 groups.

We propose that in men with MS, high E2 defines a distinct sub-phenotype, which manifests significantly higher BMI, higher fat excess and more central fat, that do not translate into further impairment in glucose control, serum lipids or arterial properties (hypertension/PWV/endothelial function). No E2 (or BT)-related feature clustering could be detected in postmenopausal women with MS (n=70). Thus, in men with the MS, high E2 is linked to higher fat mass, but E2 per se, or a yet to be defined covariate of E2, may provide protection from some of the ill effects of excess weight.

The Role of FABP4 in the Pathophysiology of Gestational Diabetes

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The pathophysiology of insulin resistance development during pregnancy is not fully understood. Recently the adipokine fatty acid-binding protein 4 (FABP4 or aP2) was found to have a key role in glucose and lipid metabolism, therefore implicated in the pathophysiology of insulin resistance and diabetes. In this work we aimed to determine whether circulating maternal FABP4 level is associated with insulin resistance indices during pregnancy. Fasting serum glucose, insulin and FABP4 levels were determined in three different cohorts: normoglycemic non-pregnant women (n=45), normoglycemic pregnant women (n=55); and in women with gestational diabetes mellitus (GDM, n=14) treated with insulin. We showed that FABP4 levels were significantly higher in women with GDM as compared to normoglycemic pregnant women (20.1, IQR: 14.6-22.6 ng/ml, vs. 10.0, IQR: 7.8-13.9 ng/ml respectively, p=0.01). In a pooled analysis, FABP4 levels were higher in obese vs. lean women (17.5, IQR: 13.8-21.6 ng/ml vs. 10.7, IQR: 7.8-13.4 ng/ml, respectively, p=0.02). BMI was similarly associated with increased FABP4 levels in non-pregnant women as well. In logistic regression analysis adjusted for maternal age, BMI, glucose and insulin concentrations, the presence of GDM was independently and significantly associated with maternal FABP4 (P=0.027). FABP4 level was an independent biomarker for insulin resistance even among normoglycemic pregnant women, and was positively correlated with both HOMA2-IR (r=0.49, p=0.003), and with HOMA2%B (r=0.38, p=0.027). A rapid decline in FABP4 to a median value of 8.6 ng/ml (IQR: 5.6-16.2, p=0.004) was observed in the immediate post-partum period (day 3). In summary, we demonstrated a direct correlation between circulating maternal FABP4 levels and insulin resistance during pregnancy, which is highest in GDM. Moreover FABP4 rapidly declined following delivery, coinciding with a marked improvement in insulin sensitivity. Takentogether, FABP4 is suggested as a novel adipokine which may be implicated in the pathophysiology of pregnancy related insulin resistance.

The effect of ethnic origin on Gestational Diabetes Mellitus in a university affiliated hospital in the center of Israel.

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Objectives: The aim of this study was to evaluate maternal and neonatal outcome in women with gestational diabetes mellitus (GDM) among ethnic populations in one community hospital, located in the center of Israel.

Methods: This is a retrospective cohort study based on computerized medical records of high risk outpatient-clinic GDM patients at Assaf Harofeh Medical Center between 2005-2015.

Results: The study included 1332 women: 86% Non-Ethiopian Jews, 6.2% Arabs and 4.7% Ethiopian women. Ethiopian women had a lower pre-pregnancy and pre-delivery weight compared to non-Ethiopians (62kg±9.9 for Ethiopians vs 73kg±16 for Jews and 75kg±16 for Arabs before pregnancy and 72kg± 8.6 for Ethiopians vs 84kg±16 for Jews and 86kg±15 for Arabs before delivery, p0.01). There were no differences in weight gain among the groups (9.5kg±5.7, 11.9kg±7.4 and 11.6±7 for Ethiopians, non-Ethiopian Jews and Arabs respectively p=0.105). Neonates of Ethiopian mothers were smaller than those of Arab mothers (3093gr±604 vs 3341gr±562 p=0.029) and tended to be smaller than non-Ethiopian Jewish neonates (3254±552 p=0.082). Neonatal macrosomia was evident in 110 babies: 3.2% for Ethiopians, 8.4% for non-Ethiopian Jews and 8.6% for Arabs, although the differences were not statistically significant (p=0.32). The rate of cesarean section (C-section) was not different between groups: 45.3% for non- Ethiopian Jews, 39.8% for Arabs and 45% for Ethiopian women (p=0.41). Among women undergoing C-section, neonatal weight was significantly lower among Ethiopian women compared with non- Ethiopian Jews (3296±639 vs 2956 ±655 p=0.024) and compared with Arabs (3535±668 p=0.002).

Conclusions: In Israel, ethnical diversity has maternal and fetal implications in women with GDM. In the current study, although C-section rates were similar, neonatal weight was overall smaller in Ethiopian women. Further studies are needed in order to define traits of GDM unique to this sub-population.

Post-Bariatric Surgery Hypoglycemia: Report of a Single Center

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Abstract

Background: Bariatric surgery is the most efficient long- term weight loss strategy, resulting in decreased morbidity and mortality.

Hypoglycemia is recognized as one of the severe complications after Roux-en-Y gastric bypass (RYGB) surgery. However, recent studies report occurrence of hypoglycemia also after Laparoscopic sleeve gastrectomy (LSG).

Objectives: To describe our experience with 19 post-bariatric surgery patients referred to our center for evaluating symptoms suggestive of hypoglycemia.

Methods: The subjects underwent Meal Test (Ensure Plus). Serum glucose, insulin and c-peptide were measured at baseline and at 30, 60, 90, 120 and 180 minutes post Ensure ingestion. Anthropometric and metabolic parameters were evaluated.

Results: 13 female and 6 male patients were included in this study. 15 of these patients, mean age 45.6±11.9 years, had documented hypoglycemia (glucose ≤65 mg/dl). Six underwent LSG, and the rest, RYGB surgery. Six patients had diabetes prior to surgery. Mean BMI was 42.4±3.7 before surgery and 29 ±4.3 kg/m^2 at time of evaluation.

Hypoglycemic symptoms started 12 ± 10 months after surgery. Hypoglycemia was detected 90-120 minutes post- challenge, mean 52.7±10.1 mg/dl and was preceded by marked elevation of C-peptide and insulin 30-60 minutes post- challenge.

The lowest glucose levels in patients after RYGB surgery and LSG were: 46.3±13.4 (range 25-65) and 48.9±11.8 (range 40-62) mg/dl respectively (P= non-significant).

Conclusions: Our study confirms recent data that significant postprandial hypoglycemia can occur also after LSG.

A new obesity phenotype in older (≥ 65yrs) subjects: the co-presence of frailty and functional limitations is linked to central obesity

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Introduction: Increased muscle fat and decreased muscle mass, strength and function are present in the elderly. Whether or not variation in the phenotype of obesity in older subjects is related to frailty and functional limitations is presently unclear. **Aim:** To evaluate the mutual association of obesity and obesity phenotypes with frailty and functional limitations. **Methods:** We applied a post hoc estimation model to detect frail prone subjects and direct questionnaire to assess functional limitations using a cross-sectional population-based national Health and Nutrition Survey in community dwelling Israeli subjects (MABAT Zahav, 2005-6) aged 65 or more (n=1845). Data were analyzed according to body mass index (BMI) and waist circumference (WC). **Results:** BMI was 1.42 kg/m2 higher in frailty-prone (FP) subjects and 4.58 kg/m2 higher in subjects who had several functional limitations. WC was 3.04cm larger in FP subjects and 7.44 cm larger in subjects with functional limitations, respectively. High WC was 1) linked to functional limitations in subjects with either high (OR 2.04) or low BMI (OR 2.15); 2) associated with increased propensity for estimated likelihood of frailty in all BMI classes, particularly in those with high BMI. Strikingly, though, it is the co-presence of frailty/frailty likelihood ***and*** functional limitation (n=164; 9.13%) that most steeply increased as a function of WC, rising curvi-linearly from OR of 0.2 for WC of 79cm to 3.2 (16 folds) for a WC of 132cm, after adjustment for age and gender. **Conclusions:** Older subjects with high WC have increased OR for a combined phenotype of frailty with functional limitations. High WC in the elderly should be identified for early detection of individuals at-risk for this devastating, new entity of both frailty and functional incapacity, which is possibly a late sequel of obesity.

Should Bariatric Surgery be offered to Obese Patients with Type 1 Diabetes?

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Introduction

Bariatric surgery has emerged as a viable treatment option in morbidly obese individuals with type 2 diabetes. Concomitant with societal lifestyle changes and the increased emphasis on achieving metabolic targets, there has been a rise in the number of patients with type 1 diabetes (T1D) who are obese. There is a paucity of data on the impact of bariatric surgery in T1D.

Aims

To compare diabetes control and weight change in obese patients with T1D that underwent bariatric surgery versus medically treated patients.

Methods

In this observational study, follow-up data of patients with T1D and BMI above 30kg/m^2 were retrieved from electronic files of Maccabi Health Services. Twenty-six obese subjects with T1D that underwent bariatric surgery (bariatric group) were compared with 26 obese subjects with T1D who were treated medically (control group) for: age, diabetes duration, BMI and HbA1c.

Results

Fifty-six subjects were included in the analysis: 15 males, mean age: 36.8±10.2 years, with mean diabetes duration of 15.6±9.9 years.

On median follow-up of 49 months (range 12 to 60) mean BMI significantly decreased post-operatively from 39.6±4.4 kg/m^2 to 28.2±3.7 kg/m^2 and slightly increased in the control group from 33.6±3.8 kg/m^2 to 35.6±4 kg/m^2. A significantly change of HbA1c with time was observed: glycemic control of the bariatric group improved (HbA1c changed from 8.5±0.9% at baseline to 8.0±1.1% at follow-up) while HbA1c of the control group increased (7.9±1.8% at baseline to 8.4±1.1% at follow-up).

Conclusions

Diabetes control and BMI of patients with T1D and obesity seems to deteriorate with time. Bariatric surgery leads to remarkable and sustained weight loss and improvement in glycemic control. Therefore, bariatric surgery should be offered to obese patients with T1D.

The Food Preservative Propionic Acid as a Diabetogenic and Obesogenic Factor

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Propioic acid (PA) is a potent mold inhibitor widely used as a preservative by the food industry. In mammals PA was also demonstrated to acutely increase blood glucose levels , which was attributed to increased gluconeogenic substrate availability. Here we report that acute exposure of mice to PA results in glycogenolygsis and a rapid increase in hepatic glucose release. This effect is mediated by an increase in circulating levels of both glucagon and fatty-acid binding protein 4 (FABP4 or aP2), which are fasting hormones known to increase hepatic glucose production. Furthermore, FABP4$^{-/-}$ mice as well as mice lacking the liver glucagon receptor were protected from the effects of PA. While PA does not seem to directly increase glucagon and FABP4 secretion, it activates the sympathetic nervous system (SNS) leading to increased glucagon and FABP4 release. Significant attenuation of the PA-induced increase in glucagon and FABP4 as well as preventing the hyperglycemic response could be induced by pharmacological inhibition of either norepinephrine release or Similar results were obtained in human in a randomized, double-blinded, placebo-controlled cross-over study conducted on healthy human volunteers, a mixed meal test containing PA resulted in increased post-prandial glucagon, Fabp4 and norepinephrine levels as compared to a placebo-supplemented meal, associated with compensatory hyperinsulinemia and mild hyperglycemia. Mice that were chronically exposed to PA at a dose equivalent to that used for food preservation demonstrated increased adiposity and insulin resistance. However, this effect could be prevented by treating the mice with FABP4 neutralizing antibodies or by using FABP4-deficient mice. In conclusion, the PA activates catecholamine-mediated increase in insulin counter-regulatory signals, leading to an inappropriate increase in post-prandial hepatic glucose release and compensatory hyperinsulinemia, which overtime may lead to weight gain and insulin resistance. These findings warrant careful evaluation of the metabolic consequences of chronic exposure of humans to PA-containing processed foods.

Gene Therapy for Diet- Induced Obesity with Platelet Type 12-Lipooxygenase Antisense: *In Vitro* and *In Vivo* Studies

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Background:

Lipoxygenases (LOXs) are a family of enzymes involved in oxygenation of unsaturated fatty acids as arachidonic acid linoleic acid. LOX products account for less than 1% of fatty acid metabolites in fat tissue but may participate in adipocyte signaling. We previously reported that a 12LOX product 12hydroxyeicosatetraenoic acid is produced and inhibits apoptosis in vascular smooth muscle cells.

Goals:

- Examine expression of platelet type 12 LOX (p12LOX) in adipocytes, study the knockdown of p12LOX antisense (AS) in fat cells.
- Explore the metabolic consequences of in vivo down-expression.

Setting and Model:

1) Cultured 3T3 preadipocytes and human adipocytes harvested during surgery were transfected with Adeno-Associated Virus (AAV)(1GMT) p12LOX AS. 2) In vivo studies in male C57Bl mice after 8 weeks of high fat diet.

Results:

1) in-vitro transfection with 12LOX anti-sense (AS) induced adipocyte apoptosis in cultured 3T3 cells (20% as opposed to 2% in control, $p<0.0001$) as well as in human adipocytes (30% of cells as compared to 13% in control, $p<0.0001$).

2) Injection of AAV with AS to inguinal fat pad in male C57Bl mice after 8 weeks of high fat diet. Two weeks after injection, AS mice lost significantly more weight than controls: weight loss of 4.29gr vs 2.09 gr, $p<0.05$. AS mice had lower abdominal adipose tissue mass (0.466875+/-0.225823 grams vs 0.682+/-0.176874092 grams; $p=0.012693427$) and liver mass. Analysis of adipocyte number per High Power Field (HPF) yielded significantly smaller cell size in comparison to control mice (1913.21 µm3 vs 2469.17 µm3;$p<0.001$). Glucose tolerance test was improved significantly more in the AS mice, with highly significant difference in glucose levels after treatment with 12LOX AS (area under the curve 29032.03125+/-9785.449582 mg/dl glucose vs 39745.46875+/-8159.360255 mg/dl post treatment; $p<0.05$; $n=16$, $n=12$ per group).

This study shows local intra-abdominal knockdown of 12LOX induces weight loss and improved insulin sensitivity. Further studies should be done to evaluate the precise mechanism and long term consequence of such therapy.

Hepatic CB1 Receptor Promotes Leptin Resistance via Regulating Soluble Leptin Receptor Levels

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Background: Leptin plays a major role in regulating body weight via the activation of hypothalamic leptin receptor. The soluble form of leptin receptor (SLR), secreted by the liver, regulates leptin's bioavailability and bioactivity, as demonstrated by the enhanced effects of leptin on food intake, body weight and energy expenditure in mice overexpressing SLR. Diet-induced obesity (DIO) is associated with reduced SLR levels, hyperleptinemia and increased activity of the endocannabinoid (eCB) system. Cannabinoid-1 receptor (CB_1R) blockade attenuates the obesity-associated leptin resistance. Yet, a direct regulation of SLR production by the eCB system has not been reported.

Aim: To determine the contribution of hepatic CB_1R to the expression and/or subsequent release of SLR in mice and hepatocytes, and assess their effect on leptin sensitivity.

Results: DIO in mice resulted in increased plasma leptin levels. This was accompanied by reduced hepatic expression of leptin receptor isoforms and circulating levels of SLR. These changes were reversed by a peripherally restricted CB_1R antagonist, JD5037. Furthermore, mice with either hepatic ablation or overexpression of CB_1Rs showed high or low plasma SLR levels, respectively. Evidence for direct regulation of SLR expression via CB_1R was determined in immortalized mouse hepatocytes in which stimulating CB_1R by 2-arachidonylglyceryl ether reduced SLR levels in the media, an effect that was completely reversed by JD5037.

Conclusions: These findings highlight a novel role of the hepatic CB_1R in regulating SLR levels. Increased activity of the eCB system in obesity may target hepatic CB_1R to decrease the expression and/or subsequent release of SLR into the circulation, and thus may promote hyperleptinemia and leptin resistance.

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Novel compound heterozygous truncating mutations in Phosphoglucomutase 1 gene causes galactose responsive severe hypoglycemic episodes in a patient with Pierre Robin sequence

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Introduction:

Phosphoglucomutase 1 (PGM-1) deficiency (glycogen storage disease type XIV) is a congenital disorder of glycosylation with impaired glycogen and glycan biosynthesis causing hypoglycemic episodes. Other clinical features include brachial arch manifestations, myopathy, endocrinopathies, and elevated liver function tests.

Aim:

Elucidating the substantial genetic, diagnostic and therapeutic challenges in a patient presenting with Pierre Robin sequence and severe hypoglycemic episodes.

Methods and results:

A 1.25 years old child with Pierre Robin sequence presented with frequent, fasting and postprandial hypoglycemic episodes, augmented following a nutritional switch to lactose free formula.

In spite of almost continuous feeding via PEG- glucose monitoring revealed frequent hypoglycemic episodes with relatively low glucose variations and a paradoxical decline in glucose levels from 57 mg/dl to 44 mg/dl during glucagon test.

Repeated "critical samples" did not elucidate a pathophysiologic etiology for the hypoglycemia. Transferrin Isoelectric focusing showed decreased tetrasialo-transferrins and increased asialo-, monosialo-, disialo and trisialotrasferrins indicating interrupted synthesis and processing of glycans - a highly specific pattern of PGM1 deficiency.

PGM-1 sequencing revealed compound heterozygotes mutations- p.F380fs21* (exon 7) and p.E450*(exon 9)- with early stop codons and premature protein truncation.

A trial of galactose supplementation recently reported to allow efficient glycogenesis and glycan synthesis resulted in profound clinical and biochemical improvement enabled significant pauses of 90 minutes between meals without hypoglycemia.

Conclusion:

In this unique case of recurrent hypoglycemic episodes the identification of the rare glycosylation defect - PGM-1 deficiency- enabled dramatic clinical improvement achieved by a relatively simple nutritional modification.

The Role Of MiRNAs In Maintenance Of Beta Cell Replication And Mass

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Beta cells are insulin-secreting cells in the endocrine pancreas, whose function is critical for regulating metabolism. Primarily controlled secretion of insulin by beta cells in response to glucose uptake, serves homeostatic regulation of blood glucose levels. Adult, differentiated, beta cells are largely quiescent. Beta cells might be driven into the cell division cycle by metabolic stress, which induces specific mitogenic cascades including c-Myc/E2F signaling.

MicroRNAs (miRNAs) are small, non-coding RNAs. miRNAs are involved in regulating beta cell differentiation and function and are thus critical for normal glucose homeostasis.
miR-17-92 is a family of 15 miRNAs with established roles in cell division and oncogenesis. Since miR-17-92 is intertwined into the Myc/E2F network in other context, we hypothesize that a family of microRNAs, miR-17-92, co-regulates beta cell division. Therefore, the goal of this work will be to decipher the involvement of miR-17-92 family in beta cell replication, by employing mouse genetics and molecular approaches. In order to determine the effect of miR-17-92 family on beta cells cell cycle we used immunostaining combined with confocal imaging, Real time PCR, RNA-sequencing and FACS. We also characterized the miR-17-92 knockout and overexpression mice using different physiological assays. Our unpublished data demonstrate a critical role for the miR-17-92 family in glucose homeostasis, in regulation of beta cell replication and beta cell mass. Furthermore we found that the miR-17-92 family has a unique role in beta cell proliferation. In different from cancer cells in which the miR-17-92 have a role in entrance to the cell cycle we show that in beta cells these miRNAs function in the mitotic check point regulation.

Our conclusion is that the miR-17-92 family is important for normal beta cell proliferation and therefore for maintaining normal beta cell mass and glucose homeostasis. We now investigate the functions of the specific miRNAs in the miR-17-92 cluster as gate keepers of beta cell mass in response to severe glucose stress. Once accomplished, this study should provide a framework for understanding how miRNAs co-regulate beta cell replication and metabolism.

The Role of MicroRNAs In Maintenance of Pancreatic Beta-Cell Identity

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Pancreatic β-cells are the only cells in the body capable of producing and secreting insulin in response to increase in blood glucose level. Loss of β-cells or their malfunction leads to Diabetes Mellitus, a disease rapidly becoming a world-wide epidemic. It was believed that in the course of diabetes β-cells undergo apoptosis, however studies suggest the occurrence of alternative mechanisms, in which terminally differentiated β-cells de-differentiate to a precursor state in which they fail to produce insulin.

MicroRNAs are short, non-coding RNAs that were found to play essential roles in both pancreas organogenesis and maintenance of β-cell identity. As previously demonstrated by our lab, global microRNA deletion induced hyperglycemia and reduced islet insulin levels.

The aim of my research is to further investigate the role of specific microRNAs in maintenance of β-cell function and identity. For that we profiled microRNA expression in rodent models that compromise β-cell function and evaluated their impact using *in-vitro* manipulations.

Our preliminary results demonstrate upregulation of the exocrine-specific microRNAs and downregulation of beta-cell specific microRNA in pancreatic islets from rodent models of pancreas regeneration and metabolic stress. Furthermore, their negative impact on isolated islets was confirmed by *In-vitro* trials, overexpressing or downregulating the identified miRNAs.

We further intend to evaluate the role of the identified microRNAs at the molecular and physiological level using transgenic mice harboring microRNA overexpression or knockout.

Group 2: Thyroid

Pediatric Reference Values of Thyrotropin (TSH) Should be Personalized According to Child Characteristics`

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Background:

Primary care pediatricians use thyroid function tests (TFT) as screening tests in children and adolescents with various health complaints. It is crucial to evaluate the results according to appropriate cut-offs individualized to the child characteristics. Such reference values are missing in the pediatric population.

Aim:

To determine normal TSH levels in a large cohort of healthy children.

Methods:

Data was collected from the database of Clalit Health Medical Organization ensuring more than 1.3 million children. 75,857 healthy children aged 5 to 18 years in which TFT were evaluated during 2012-2014 were included in the study. Data analyzed included: age, gender, BMI SDS, ethnicity, dispend medications, TSH, FT4 and FT3 levels.

Results:

TSH levels were significantly higher in boys compared to girls: median 2.21 mIU/L (normal range 0.83-5.25) vs. 2.11 mIU/L (0.89- 5.29), P0.0001. TSH levels were found to vary significantly according to ethnicity; TSH Ievels in the Jewish population were significantly lower compared to the Israeli Arab population: median 2.14 mIU/L (0.85-5.14) vs. 2.22 mIU/L (0.84- 5.85), P0.0001. BMI was found to significantly effect TSH levels with levels increasing as weight diverge from the normal range; median levels were 2.13 mIU/L (normal range 0.74-5.13), 2.04 mIU/L (0.79-5.05), 2.14 mIU/L (0.88-5.45), 2.37 (0.95-5.74) for children defined as underweight, normal weight, overweight and obese respectively. Age did not significantly affect TSH distribution.

Conclusions:

Our results in this uniquely large cohort show that the normal range of TSH in children is affected by gender, weight and ethnicity. Reference values should be thus individualized and modified accordingly. Such modifications will improve future clinical decision-making and treatment.

The epidemiology of thyroid dysfunction and effectiveness of TSH screening in medical inpatient

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Introduction: Thyroid function test disturbances in hospitalized patients are common and mostly attributed to stress response due to acute illness state rather than thyroidal illness. TSH test is recommended by leading endocrinology associations only with the presence of clinical suspicion. On the other hand, thyroid illness may progress slowly, especially in the elderly, thus even significant clinical dysfunction may present as an asymptomatic state. TSH testing is done in all patients hospitalized in Internal Medicine departments in Galilee Medical Center as a part of admission panel.
This study aims to determine the prevalence of major types of thyroid disturbances and to evaluate the effectiveness of thyroid function testing in patients admitted to this hospital.

Methods: A retrospective study of data retrieved from files of patients admitted to Internal Medicine departments at Galilee Medical Center between 2014-2016. 232 randomized hospitalizations with abnormal TSH blood test were tested for underlying thyroidal disturbances. Thyroidal disturbance prevalence was calculated and effectiveness of TSH screening test was estimated individually.

Results: Thyroidal disturbance prevalence in hospitalized patients was calculated:
subclinical thyrotoxicosis 2.44%, subclinical hypothyroidism 2.19%, clinical hypothyroidism 0.56% and clinical thyrotoxicosis 0.46%. Out of 9 patients with clinical thyrotoxicosis only one had corresponding elevated FT3 levels and a proper thyrotoxicosis diagnosis. The 8 remaining patients` TSH screening test disturbances were more characteristic for non-thyroidal illness and drug effects.
Out of 11 patients with clinical hypothyroidism, 55% had a known diagnosis of hypothyroidism. 65.5% of all the study patients were treated shortly before or during hospitalization with a thyroid effecting drug, mainly glucocorticoids. In 13.4% of patients, a diagnostic workup was done and in the majority of cases (61%) it was proven to be unnecessary. TSH screening was beneficial only in 9 patients (3.8%), all of whom had either known thyroidal disturbance diagnosed previously or a clear clinical symptoms necessitating TSH levels test.

Conclusions: Low efficacy is ascribed to TSH screening test by this study, as most of disturbances discovered did not require diagnostic workup and were attributed to non-thyroidal illness and drug effects. In addition, routine screening in all admitted Internal Medicine patients leads to a high rate of unnecessary diagnostic workup.

FT3 decreases through life, more in males than in females; But levels eualize in elderly

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*Context***:** Based on small studies, it is accepted that over the lifespan thyrotropin (TSH) levels are relatively stable and both free triiodothyronine (FT3) and free thyroxine (FT4) levels decline. We had the opportunity to look at age related trends in the largest database ever used for this purpose, thus facilitating a closer look at these trends and allowing a closer look at gender differences.

Objective: To examine trends in Thyrotropin and thyroid hormone levels from childhood to old-age including gender differences.

*Design and Setting***:** Examination of a large database of pediatric and adult thyroid test results drawn in community clinics from patients without known thyroid disease.

*Patients and Methods***:** free T3 (FT3), free T4 (FT4) and TSH levels from 527,564 sera taken from patients age 1 year or greater were studied. After highly extensive exclusion criteria applied in order to remove all samples that may have been taken from unhealthy people 27,940 samples remained. These were stratified by decades of age and by gender in order to investigate trends of hormonal levels over the entire lifespan. Samples for whom anthropometric data were available were stratified for body mass index (BMI).

*Main outcome measures***:** Trends of thyrotropin and thyroid hormone levels with age.

Results: FT3 decreases throughout life, significantly more so among females with equalization in the elderly. FT4 declines, to a lesser extent and more so among females than among males. Among the extreme elderly, females have higher levels of FT4. In contrast, TSH declines until age 50 years and then increases slightly among both genders with no siginificant difference between the genders.

Conclusion: This large study confirms results of smaller studies regarding trends in hormonal levels by age and gender. These data have important implications for therapy of thyroid conditions in the elderly.

Body composition, resting energy expenditure and metabolic changes

in differentiated thyroid carcinoma female patients

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***Background*:** Thyroid hormones have an important role in determining energy expenditure, body mass, and body composition. However, their effects in the state of exogenous subclinical hyperthyroidism in patients with differentiated thyroid cancer (DTC) are less conclusive.

Aim: To assess changes in body weight, body composition, resting energy expenditure (REE), respiratory quotient (RQ), metabolic parameters and relationships between these parameters and thyroid function tests in DTC female patients.

***Methods*:** This prospective observational pilot study analyzed changes in body composition, REE, and metabolic parameters of 15 DTC female patients: at initial DTC diagnosis (euthyroid state), at 2-3 weeks after thyroidectomy (hypothyroid state), at 2-3 months of levothyroxine (LT4) treatment (exogenous euthyroid state), after 6-9 months and after one year of thyroid stimulating hormone (TSH) suppressive LT4 therapy (subclinical hyperthyroid state). *Generalized estimating equation (GEE) analysis was performed to estimate the longitudinal correlations of* TT3/FT4 ratio (as an independent variable) with metabolic parameters, body composition, and REE changes (as dependent variables).

***Results*:** REE, heart rate and systolic and diastolic blood pressure were significantly higher after TSH suppressive LT4 therapy compared to the euthyroid state at the beginning of the study. *The GEE analysis revealed longitudinal negative correlations between* the TT3/FT4 ratio and systolic blood pressure (SBP); fasting blood glucose; body mass index; android fat distribution and REE; and a positive correlation with RQ.

***Conclusions*:** In TSH-suppressed DTC female patients, lower TT3/FT4 ratio longitudinally correlated with increases in SBP, a poorer metabolic profile, and abdominal fat distribution, as well as with decreased RQ. While correlations do not establish causality, these findings still highlight the importance of judicial balancing of the benefits and detriments of thyroxin-only [T4 without T3] based TSH suppression for DTC patients. More research regarding a possible benefit of T3 and T4 combined therapy for this population is needed.

Thyroid Disease in Pregnancy: A Clinical Survey Among

Endocrinologists Gynecologists and Obstetricians in Israel

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Background: The detection and treatment of thyroid disease in pregnancy is a matter of controversy. Previous surveys demonstrated variations in the clinical practices relating to the treatment and screening of maternal thyroid dysfunction.

Methods: An electronic questionnaire was e-mailed to all members of the Israeli Endocrine Society and members of the Israel Society of Obstetrics and Gynecology (OB/GY). Questionnaires included demographic data and clinical scenarios with questions regarding the screening and management of pregnant women with subclinical hypothyroidism (SCH), hypothyroxinemia and a palpable thyroid nodule. Questionnaire for OB/GY was slightly modified.

Results*:* We received 90 responses from endocrinologist and 42 responses from OB/GY. Among endocrinologists, 39% would repeat a TSH test of 2.9 mU/L with normal FT4 and treat with thyroxine if the second result were above 2.5 mU/L. Among OB/GY, 73% would manage a woman with SCH at the beginning of her pregnancy by themselves and only 22% would start thyroxine after a first TSH result above 2.5 mU/L. Forty two and 44% endocrinologists and OB/GY respectively would neither treat nor monitor women with hypothyroxinemia in pregnancy. Concerning screening, 57% and 71% endocrinologists and OB/GY respectively recommend screening for thyroid dysfunction in every woman at the beginning of her pregnancy. Among endocrinologists, 54% would order an ultrasound for a palpable thyroid nodule and perform a fine needle aspiration only for suspicious lesions.

Conclusions: The medical approach to thyroid disease in pregnant women remains a matter of controversy. Our survey supports the need for larger and prospective clinical studies.

Management of Relapsing Graves: A Clinical Survey Among Endocrinologists in Israel

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Background: The management of relapsing Graves` disease is controversial. Previous surveys from different regions in the world demonstrated variations in the clinical practices of patients with graves' disease relapse.

Methods: To determine management pattern among endocrinologists in Israel an electronic questionnaire was e-mailed to all members of the Israeli Endocrine Society. Questionnaires included demographic data and clinical scenarios with questions regarding the treatment and follow up of patients with relapsing graves' disease.

Results*:* We received 98 responses from Israeli endocrinologists. 42 (43%) males and 56 (57%) females. 41.8% had board certificate for more than 10 years. 72.4% responders work in hospital environment and 26.5% work in community clinics. 61.2% see more than 10 thyroid patients in clinic per week. When managing Graves' relapse following ATD treatment in a young male, 68% would restart ATD (98% mercaptizole) and 32% would refer to RAI treatment. Interestingly, endocrinologist who treat more thyroid patients (more than 10/week) tend to choose ATD over RAI (p=0.04). In case of recurrent graves' and ophtalmopaty 50% would continue ATD, 22.4% would recommend RAI treatment and 27.6% surgery. Most endocrinologists (56%) would continue ATD for 12-24 months. 75% would monitor CBC and liver function (39% for the first month and 36% for 6 months). 44% would recommend routine neck US, and 19.3% would recommend routine DEXA. In a case of thyrotoxicosis due to 3 cm toxic nodule tirads 4a most endocrinologists (70%) would refer to RAI ablation, 46.4% without FNA and 23.7% with FNA. No significant difference was found in correlation with gender, years of board certificate, or work environment.

Conclusions: In Israel, most endocrinologists would treat graves' disease relapse with ATD and not RAI or surgery. Clinical decisions are influenced by the number of thyroid patients seen in clinic per week.

Plasmapheresis in treating severe Graves` thyrotoxicosis: A case report

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Context: An agranulocytosis secondary to methimazole causes a challenge in the treatment of patient with severe thyrotoxicosis. There is extreme paucity of information regarding the mechanistic and clinical effects of plasmapheresis in the treatment of Graves` thyrotoxicosis.

Objective: The aim of the study was to describe and discuss the case of plasmapheresis treatment as a bridge to surgery in a patient with pre-storm Graves` thyrotoxicosis.

Patient and Methods: A 46-year-old Arab woman developed Graves` ophthalmopathy, dermopathy and hyperthyroidism at the age of 23y and was since partially-complaint to methimazole therapy. She was re-started on 60mg/day of methimazole due to exacerbation of thyrotoxicosis manifested by a 10kg weight-loss, exacerbation of dyspnea, weakness, and tachycardia. The drug was withdrawn because of agranulocytosis and fever. FT4 was 129pmol/l and FT3 34pmol/l with Radioactive Iodine Uptake 90% post-2hours and 60% post-24hours. In preparation for thyroidectomy she was treated with four daily plasmaperesis cycles, high dose dexamethasone, propranolol, cholestyramine, vitamin D3 and calcium. A continues decrease in thyroglobulin, anti-TPO and Thyroid-stimulating immunoglobulins [TSI] titers was documented following each cycle of plasmapheresis, although TSI bio-activity remained significantly elevated. FT4 dropped to 65.5pmol/l and FT3 to 12.6pmol/l. However FT3 increased again to 17.7pmol/l within few hours after the 4th plasmaperesis cycle and 2 doses of Lugol`s solution were added causing brisk FT3 dropping to 9.4pmol/l. She was then successfully operated with a normalization of FT3 within hours.

Conclusion: Similar to previous reports with amiodarone-induced thyrotoxicosis, this case suggests that plasmapheresis is effective in rapid reduction of free thyroid hormones. The transient effect is likely due to failure of the plasmapheresis to eliminate the potent TSH-receptor activating immunoglobulins. In accordance with the 2016 ATA guidelines for management of thyrotoxicosis (Rec. 26), iodine solution can be used even without thionamides in the immediate pre-operative period to ameliorate the thyrotoxicosis.

Approach to a Monofocal Papillary Thyroid Cancer: A Clinical Survey Among Adult Endocrinologists and Surgeons in Israel.

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Background: New ATA guidelines for management of thyroid nodules recommend considering hemithyroidectomy for some PTC tumors up to 4 cm. We aim to check the impact of the new guidelines on physician`s decision making. **Methods**: An electronic questionnaire was e-mailed to endocrinologists and ENT surgeons including demographic data and an index case: A 26 y.o. healthy women with a 3 cm Bethesda III solitary nodule. **Results***:* Responders rate was 62% (134/216), 93 endocrinologists and 41 surgeons. For this case 46.2% would repeat FNA, 24.6% would perform molecular analysis and 22.4% refer directly to surgery. If repeated FNA remain B3, 49% would proceed to surgery, 18% molecular analysis and 32% follow up only. If repeated FNA was B6, 58.5% would recommend total (TT) and 41.5% hemithyroidectomy (HT). If PTC is pathologically confirmed after HT, 41.6 % would recommend completion, 65.4% of them followed by RAI therapy. While 53% will recommend HT for tumors up to 4 cm in the index case, 35% will recommend TT already above 2 cm. Variables favoring TT were family history (89%) and scalp irradiation (95%). Only 17% and 25% responders would prefer TT in the presence of small benign contralateral tumor or Hashimotos, respectively. In patients with normal US and undetectable Tg one year after TT and RAI, 63% would perform Tg stimulation but only 12% would order iodine scan. For recurrence in two (13 and 9 mm) LNs after TT and RAI, 56% would recommend reoperation, 17% RAI and 26% active surveillance. Main differences between endocrinologists and ENT were: iodine after completion thyroidectomy (9.3 vs 25.7%), HT for 4 cm tumor (79 vs 46%) and impact of Hashimoto and age (18 vs 37% and 18 vs 36%, respectively). **Conclusions**: Despite the new ATA guidelines, the approach to a near 4 cm monofocal low risk PTC tumor remains controversial.

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) at a Tertiary Center in a Country with High Rates of Thyroid Cancer

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Given variable reporting of Bethesda classes III and IV between centers, it has been suggested that each institution establishes its own frame of reference.

Aims: To assess the relative frequency of Bethesda III and IV categories among FNAs performed at our center between January 2013 and December 2015, and to determine the malignancy rate in each category.

Results: 2,915 FNAs, sampled a total of 3,676 nodules in 2,666 subjects (2,140 W/526 M, aged 58 y, range 18-87). Of these, 248 nodules returned Bethesda III (5.6%), and 108 (4.0%) Bethesda IV. Follow-up was available for 96 of these Bethesda III and IV nodules together (27%).

Of the 59 nodules classified as Bethesda III, 46 were reaspirated. 24 were reclassified as class II (52%), 13 (22%) remained class III, and 5 (11%) were reclassified as IV. Surgery was done on 18 of these initially Bethesda III nodules (30.5%). A diagnosis of thyroid cancer was made in 4 cases (22% of the operated cases). Afirma® was used on 7 class III nodules. It ruled out malignancy in 5 cases and was suspicious in 2. At surgery only one of these 2 nodules was cancerous. For the 59 class III nodules, a firm diagnosis of cancer was established in only 4 (6.8%).

Of the 37 nodules initially classified as Bethesda IV, only 24 were referred to surgery (65%). 13 turned were benign (54%), 11 were cancerous. Thus a firm diagnosis of malignancy was established in about 30% of class IV nodules.

Conclusions: In this sample of FNAs, we noted relatively low rates of category III and IV reporting. Moreover, referrals for surgery were less frequent than expected. Nevertheless, both the frequency of Bethesda III and IV reporting, and the malignancy rate in each category, are in line with the original BSRTC publication. As our country has one of the highest rates of thyroid cancer in the world, these figures do not suggest underdiagnosis of thyroid cancer, rather they indicate liberal referrals to FNA. These figures could change with the implementation of the newer guidelines.

Trends of second primary malignancy in patients with thyroid cancer: a population-based cohort study in Israel

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***Background*:** Thyroid cancer (TC) is the most common endocrine malignancy. TC patients are often young, have a good prognosis and a low disease-related mortality rate.

Aim: Our objectives were to determine the incidence, risk and types of SPM during the years 1980 to 2011, and to assess SPM time trends in a cohort of Israeli TC patients.

***Methods*:** Data were derived from the Israel National Cancer Registry. Primary TC patients diagnosed during 1980-2009 were followed-up for SPM incidence until December 31, 2011. Standardized incidence ratios (SIRs) of observed to expected SPM (based on the general population rates) were calculated.

***Results*:** 11,538 TC patients were included in the study cohort. Records of 1032 patients with SPM one year and more from TC diagnosis were analyzed. The incidence rate of SPM in TC patients was 8.9%. SIR for all-site SPM was 1.23 (95% CI 1.08-1.35) in males and 1.19 (95% CI1.10-1.27) in females. SIRs for tumors of the urinary system and prostate were significantly elevated in males, as were SIRs for tumors of the brain, urinary system, breast and lung in females. Variables associated with increased risk of developing SPMs included: a younger age at TC diagnosis, a shorter latency period, being born in Asia/Africa for both genders, and being born in Israel for females. Compared to the general population, a sub-analysis by TC diagnosis during 1980-1995 and 1996-2009 disclosed a higher SPM incidence for the latter time period in males and for both time periods, with a slightly higher SIR for the latter time period, in females.

***Conclusions*:** The overall risk of SPM in Israeli TC patients was significantly greater for both genders compared with the general population, thus identifying TC patients as a high-risk group, and calling for caretakers to apply specific follow-up guidelines.

The Impact of Minimal Extra-Thyroidal Extension on Outcome in Differentiated Thyroid Cancer: Systematic Review and Meta-analysis

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Background: Minimal extra-thyroidal extension (mETE) in differentiated thyroid cancer (DTC) patients was defined as an intermediate risk feature in the 2015 American Thyroid Association (ATA) guidelines. However, controversy persists as several studies suggested mETE has little effect on disease outcome.

Aim: To assess the impact of mETE on DTC patients` outcome.

Methods: Systematic review and meta-analysis of retrospective controlled trials comparing DTC patients with and without mETE. Outcome measures included recurrent or persistent disease and disease-related mortality.

Results: Thirteen studies including 22,472 patients were included, with a median follow-up of 72 months. Data on patients with N0 disease was reported in 6 studies, and N0+N1 in 10 studies (3 included both analyses). Studies were heterogeneous in terms of lymph node (N) involvement at baseline, mETE definition, type of surgery, and the rate of radioiodine ablation. Minimal ETE in patients with N0 disease was associated with increased risk of recurrence (7 studies, OR 1.73, 95%CI 1.03-2.92). This difference was mostly due to one large outlier study (Chereau 2014), whereas mETE did not confer increased risk in the other 6 studies (OR 1.37, 95%CI 0.74-2.53). In patients with mixed N0+N1 disease, mETE resulted in a significantly higher risk of recurrence (8 studies, OR 1.7, 95%CI 1.33-2.17, with high heterogeneity I^2=67%). Sub-analysis for patients with micro-PTC did not show a significant impact of minimal ETE (4 studies, OR 1.74, 95%CI 0.98-3.12). Minimal ETE had no impact on disease related mortality (8 studies, OR 0.5, 95%CI 0.11-2.21, I^2=0%).

Conclusion: Current data supports the 2015 ATA guidelines classifying mETE as an intermediate risk feature, except for patients with micro-PTC. However, data quality is poor and further studies are required to assess the prognostic effect of mETE, especially in patients with N0 disease, with the use of standardized definition of mETE, and with proper adjustment for baseline characteristics.

Be aware of the patient with thyroid benign follicular lesions and a rising thyroglobulin level

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Background. The pathological diagnosis of thyroid follicular/Hurtle cell adenoma relies on the absence of capsular or vascular invasion. However, the differentiation between these benign lesions and encapsulated thyroid carcinoma of follicular origin may be challenging.

Materials. The Rabin Medical Center Thyroid Cancer Registry was screened for patients with metastatic differentiated thyroid carcinoma (DTC) who underwent thyroidectomy in 1970-2014 and were initially diagnosed with benign follicular/Hurthle cell adenoma

Results. We identified seven patients who had undergone thyroidectomy 2-37 years before the detection of metastatic DTC lesions. The original pathological diagnosis was thyroid follicular adenoma in four patients and thyroid Hurthle cell adenoma in three. Five patients were eventually diagnosed with bone metastases, of whom one also had lung metastases and one, liver metastases. One patient had both cervical and lung metastases, and one had only metastatic neck lymph nodes. Completion thyroidectomy pathology /revision, performed in four patients, revealed encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) in all them. These included three patients in whom capsular invasion was detected retrospectively and only one with evidence of vascular invasion. All seven patients had high levels of thyroglobulin at diagnosis of metastatic DTC.

Conclusion. Pathological misclassification of follicular thyroid lesions as benign may lead to progressive disseminated DTC. The exclusion of thyroid cancer warrants a thorough evaluation of the follicular specimens by an experienced pathologist. To avoid the risks of misdiagnosis, we suggest that patients with a diagnosis of thyroid follicular/Hurthle cell adenomas be followed with repeated thyroglobulin measurements.

The Impact of Age and Gender on Medullary Thyroid Cancer Presentation and Prognosis -An Israeli Multicenter Study

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Background: Data regarding the possible impact of gender and age on medullary thyroid cancer (MTC) presentation and prognosis is limited. Although older age and male sex were found to correlate with poorer prognosis in some studies, this association may reflect differences in MTC presentation between sex and age groups, or a mixture of hereditary and sporadic MTC forms.

Objective: To evaluate the impact of age and sex on the presentation and outcomes of MTC.

Methods: Epidemiologic and clinical data of MTC patients was extracted from a joint registry of four medical centers in Israel. Patients were stratified according to their gender and age at the time of MTC diagnosis (45 years and ≥45 years).

Results: The study included 157 MTC patients (82 females, age 49.1±18.5, median 55.5), followed for 10.9±10 years. Female gender was associated with smaller tumor size (22.4mm vs. 29.4 mm, p=0.043), lower rate of lymph nodes involvement (46.5% vs. 65.1%, p=0.037) and distant metastases (13% vs. 29.9%, p=0.021). Although females achieved higher cure rate (49.4% vs. 29.3%, p=0.022), disease related mortality and all cause mortality did not differ between genders. As expected, patients aged 45 year at diagnosis had higher rates of hereditary familial forms of MTC (43.3% vs. 2.4%, p0.0001). Analysis of the sporadic MTC group (n=115) revealed association between younger age at diagnosis and larger tumor size (33.2mm vs. 24.6mm. p=0.062), higher number of metastatic lymph nodes (14.8 vs. 6.4, p=0.011) and more therapeutic interventions (60.0% vs. 32.4%, p=0.014). However, cure rate and disease related mortality were similar between the age groups.

Conclusions: In this MTC cohort female patients presented with milder disease and achieved higher cure rates than males, however with no impact on mortality. Age 45 years was associated with milder MTC presentation in the sporadic MTC patients, with no influence on outcomes.

The Role of Hepatic Trans-Arterial Chemoembolization in Metastatic Medullary Thyroid Carcinoma: A Specialist Center Experience and Review of the Literature

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Introduction: Liver metastases are relatively common in patients with metastatic medullary thyroid carcinoma (MTC), carrying a negative impact on disease prognosis. The options for selective therapy of liver metastases in MTC patients are limited to catheter guided procedures such as trans-arterial chemoembolization (TACE). Data regarding the effectiveness and safety of this procedure in MTC is limited. **Aim(s):** To explore the clinical outcome, survival and safety profile of TACE for liver metastases in a group of MTC patients. **Materials and methods:** Retrospective case series of patients treated at a single tertiary university medical centre from 2005 to 2015. **Results:** Seven consecutive patients (mean age 64.5±10.9 years, 5 female) with histologically confirmed MTC with liver metastases were included. Metastatic involvement of the liver was less than 50% of the liver volume in all patients. The median size of the largest liver lesion was 40±6.9 mm. The patients underwent in total 20 sessions of TACE. Clinical improvement as well as tumor response (PR) were observed in all patients. The median time to tumor progression was 38 months (range 8-126). Three patients were still alive at the end of the follow-up period (a median overall survival rate of 57 ± 44 months). **Conclusion:** TACE in MTC patients with hepatic metastases is usually well tolerated and induces both clinical improvement and tumor response for prolonged periods of time in the majority of patients.

Severe Hypocalcaemia due to Autoimmune Enteropathy in a Girl with Autoimmune Polyglandular Syndrome Type 1

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Autoimmune polyglandular syndrome type 1 (APS1) is an autosomal recessive disorder with the classic triad of polyendocrinopathy, mucocutaneous candidiasis and ectodermal dystrophy (APECED). It is caused by a loss-of-function mutation in the *AIRE* gene encoding the autoimmune regulator.Although gastrointestinal manifestations occur in 25% of APECED patients, there is little awareness of them. We present a 14-year-old girl, born to consanguineous Arab Christian parents, who first presented at the age of 7 years with hypocalcaemia and oral candidiasis, Low serum calcium with undetectable PTH levels confirmed the diagnosis of hypoparathyroidism. In addition, she had vitiligo, partial adrenal insufficiency and euthyroid autoimmune thyroiditis. Over the years, diabetes mellitus type 1 and primary ovarian insufficiency developed. Molecular analysis revealed a homozygous mutation in *AIRE* (c.47CT, p.T16M). At the age of 9 years, she developed severe diarrhea and steatorrhea, along with severe hypocalcaemia that was unresponsive to high oral doses of calcium and αD_3; only intravenous calcitriol maintained serum calcium levels. The workup for intestinal and pancreatic malabsorption was negative. Endoscopy revealed normal upper and lower GI tract biopsies.Only further staining with chromogranin A revealed a total lack of chromogranin A indicating severe damage to enteroendocrine cells. Tryptophan hydroxylase autoantibodies have been shown to lead to total absence of enterochromaffin cells in the mucosa of the small bowel in patients with APECED. Tryptophan hydroxylase is an intestinal autoantigen expressed in serotonin-producing cells in the central nervous system and intestine. Autoimmune enteropathy is an important manifestation of APS1 that may lead to protracted diarrhea and malabsorption, and consequently to severe hypocalcaemia that is unresponsive to conventional therapy. Our findings indicate that chromogranin A immunostaining should be systematically performed whenever intestinal biopsies are obtained in a patient diagnosed with or suspected of having APECED.

Three Generations of an Israeli Family Diagnosed With Autosomal Dominant Activating Mutation of the Calcium Sensing Receptor (CaSR) Gene

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Introduction: Autosomal dominant hypoparathyroidism (ADH) is characterized by hypocalcemia and hypercalciuria due to calcium-sensing receptor (CaSR) mutations. It was recently also described in G protein subunit alpha 11 mutations. It is a much rarer disease than its mirror image familial hypocalciuric hypercalcemia (FHH).

Aim We describe herein the clinical presentation and the diagnosis of ADH in a three generation of an Israeli family.

Methods/patients: The proband was a newborn preterm male who presented with hypocalcemia (calcium 7.3 mg/dl normal range7.3-9.2), relative hypercalciuria (calcium/creatinine 2 normal range 0.07-0.8), magnesium (1.8 mg/dl normal range 1.2-2), vitamin D (41.7nmol/L normal range 75-125) and relatively low parathormone level (26.4ng/L normal range10-65). He was treated with calcium and vitamin D supplementation. His dizygote twin brother was normocalcemic. His father and his paternal grandfather were found more than 10 years before the proband was born to be hypocalcemic with hypercalciuria and were treated by calcium and vitamin D supplementation.

Results:DNA sequencing of CaSR gene identified a missense activating mutation c.2488GA - p.G830S in exon 7 of calcium sensing-receptor gene. The medical treatment was gradually stopped in thee proband and his father and paternal grandfather without any clinical manifestations.

Conclusion: ADH characterized by hypercalciuria and hypocalcemia due to a mutation in the calcium-sensing receptor gene was diagnosed in three generations of an Israeli family. To our knowledge this is the first Israeli family officially diagnosed in an Israeli laboratory with this rare disorder. We suggest that considering testing first degree relatives for calcium levels in blood and urine and DNA sequencing may have a role in the diagnosis of hereditary diseases with implications regarding medical therapy and follow-up.

Elevated ferritin and circulating osteoprotegerin levels as independent predictors of hip fracture in postmenopausal women admitted for fragility fracture.

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Background: Identification of risk factors may help us to understand the pathogenesis of osteoporotic hip fracture as well as to formulate development of better diagnostic, prevention and treatment strategies. The present study was designed to determine the impact of multiple metabolic risk factors such as markers of systemic inflammation (C-reactive protein), immune responses- acute phase reactants (ferritin), insulin resistance (HOMA-IR) and bone remodeling (osteoprotegerin, OPG), for the prediction of hip fractures in postmenopausal osteoporotic women.

Methods: The study group consisted of 115 postmenopausal women divided into two groups: Group 1 consisted of 49 women hospitalized in the Orthopedic Department, Wolfson Medical Center for the diagnosis of non traumatic hip fracture and Group 2 contained 66 postmenopausal osteoporotic women without a history of hip fracture. Metabolic parameters were determined.

Results: Circulating OPG was significantly higher in Group 1 than in Group 2 (205.2+/-177.1 vs 60.0=/-22.3, p0.0001). While levels of hemoglobin (Hbg) as well as MCV and MCH did not differ between groups, circulating ferritin was significantly increased in Group 1 compared to the control Group 2 (217.9+/-195.1 vs 49.7+/-31.3, p0.0001).In multiple linear regression analysis, which explains about 40% of the variability in CRP, 42% in OPG, and 28% in ferritin, significant by-group differences in terms of these parameters persisted even after adjustment.

Conclusions: Elevated serum ferritin concentrations and bone remodeling marker, osteoprotegerin, are independent predictors of hip fracture in postmenopausal women hospitalized for fragility fracture.

Bone Mineral Density in Hospital Male Physicians Over the Age of 65

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Background: Hospital physicians are indoor workers, with higher prevalence of 25(OH) vitamin D deficiency as compared to community-based physicians. The correlation between vitamin D deficiency and osteoporosis later in life has not been fully studied, and bone mineral density (BMD) in elderly hospital physicians has not been systematically examined.

Methods: A cross-sectional study measuring BMD in hospital male physicians aged 65 and older was carried out. BMD was measured at the hip, spine and distal forearm. FRAX analysis with BMD was carried out, using the IOF recommended FRAX cutoffs for treatment (10-year probability of hip fracture ≥3% and 10-year probability of major osteoporotic fracture ≥20%).

Results: 51 male physicians, employees and pensioners, participated in our study. The mean age was 71 years (median 69 years; range 65-86), all of them naive to specific treatment for osteoporosis. 14/51(27%) had osteoporosis, 7 of them defined only by distal forearm examination. 29 (56%) had osteopenia, 4 of them defined only by distal forearm examination. According to their FRAX score, 9 of the osteopenic examinees had high risk of major osteoporotic fracture and/or hip fracture.

Conclusion: In elderly hospital-based male physicians, the prevalence of osteoporosis is higher than expected. After adding the FRAX score results, 45% of the physicians would require specific treatment for fracture prevention, according to customary international clinical guidelines. Using only hip and spine BMD, 31% would require treatment. Based on our data we suggest screening elderly physicians for osteoporosis.

Hypercalcemia of pregnancy

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Background: Hypercalcemia can be hazardous during pregnancy, most cases being due to primary hyperparathyroidism. We report a case of hypercalcemia with suppressed PTH levels necessitating treatment with bisphosphonates during pregnancy.

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

Case presentation: A 38-year-old woman at the 26th week gestation was admitted because of symptomatic hypercalcemia. Her first pregnancy was uneventful. She did not take any medication that could influence her calcium levels. Physical examination was unremarkable. Laboratory tests on admission were: calcium 12.7 mg/dl (8.5-10.5 mg/ dl), albumin 3.6 mg/dL (3.5-5.2 g/dl) magnesium 1.2 mg/dl (1.8-2.6 mg/dl), phosphorus 1.8 mg/dl (2.5-4.5 mg/dl) and PTH on 3 consecutive tests 1.2, 1.3, 1.2 pg/ml (15-65 pg/ml). Her 24h urine calcium was 900 mg, 25-OH-D 40 ng/ml (30-58 ng/ml) and 1,25-OH-D 99 pg/ml (16-80 pg/ml). Thyroid function tests and ACE levels were normal. Abdominal ultrasound revealed multiple hypervascular liver lesions consistent with hemangiomas by MRI. Breast and neck ultrasound were normal and chest CT revealed few non-significant 0.3-0.7 cm pulmonary nodules with no change on 3 months' interval. She was treated with isotonic saline, loop diuretics and calcitonin. Despite this treatment, calcium levels remained high (14.1 mg/dl) and pamidronate was initiated. On 35th week gestation she underwent a cesarean section complicated by hypocalcemia of the newborn. Eight weeks after delivery her calcium levels are 9.4 mg/dL, phosphorus 3.4, 1,25-OH-D 49 mg/dl and PTH 18 mg/dl.

Conclusion: According to the extensive workup and the post-partum normalization of PTH and calcium levels we conclude that excessive secretion of placental PTHrP was the cause of hypercalcemia in this patient. No significant adverse effect of bisphosphonate on the mother or baby were seen on the short term follow up, except transient hypocalcemia of the newborn that can also be attributed to mother's hypercalcemia.

Successful Short-Term Growth Hormone Treatment For a Rare Bone Dysplasia

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Introduction

Cleidocranial dysplasia (CCD; OMIM 119600), a rare autosomal dominant bone dysplasia, is characterized by delayed closure of cranial sutures, hypoplastic clavicles, short stature, and dental anomalies. We report on four children with CCD and extreme short stature who were successfully treated with growth hormone (GH) in our clinic. To the best of our knowledge, this is the first report of GH therapy for treatment of short stature in children with CCD.

Patients and results

Four children with CCD (2 boys, 2 prepubertal) were treated with GH. Patients' characteristics are shown in Table 1. Their average age at initiation of treatment was 10.8±1.96 years, bone age 10 ±1.68, height-SDS (Ht-SDS) was -3.05 ±0.18 and their pretreatment growth velocity 4.2 ±0.42 cm\year. By the end of the first year of treatment their growth velocity improved to 10+1.36 cm\year and their Ht-SDS to -2.2 ±0.35 . GH dose was 0.05 mg/kg/d. Figure 1 illustrates growth curve of one of the patients over a two year period of treatment.

Conclusions

The results suggest that short-term GH therapy is effective for treatment of short stature in children with this rare bone dysplasia. Marked improvement of growth velocity was observed for the 1st year of treatment, similar to that observed in children with GH deficiency and idiopathic short stature. We conclude that GH therapy should be considered in short patients with CCD , and possibly for other bone dysplasias for which it has not previously been
considered.

Table 1 – Patients Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4.	Average
Gender	M	F	F	M	
Age at initiation of GH treatment (yr)	9 + 6/12	12 + 8/12	8 + 8/12	12+4/12	
Height SDS at initiation of treatment	-3.05	-2.86	-3.3	-3.1	-3.05 ±0.18
Tanner pubertal stage at initiation of GH treatment	1	2	1	2	
Bone age at initiation of GH treatment (yr)	9 + 6/12	10 + 6/12	8	12	10 ±1.68
Current duration of GH treatment (months)	32	18	17	8	
Pre GH treatment growth velocity (cm/yr)	4.5	4.5	4.3	3.6	10 ±1.68
First year treatment growth velocity (cm/yr)	9.8	11.3	8.2	10.8	10.02 ±1.36
Height SDS after 1 yr treatment	-2.1	-1.9	-2.42	-2.7	-2.27 ±0.35

Tertiary center experience with fibrous dysplasia patients: clinical variables and medical treatment

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Fibrous dysplasia (FD) is a rare sporadic metabolic bone disease with a heterogeneous presentation ranging from asymptomatic incidental finding to a debilitating disease causing pain, deformities and fractures. Treatment varies according to the clinical picture and includes observation, surgery or bisphosphonates (BP).

Due to the rarity of this disorder, the information regarding treatment is limited to cases and small series, most of them reported treatment with pamidronate. One placebo controlled prospective trial examined high dose alendronate with disappointing results. Scarce data exists regarding treatment with zoledronic acid.

Our goal was to summarize the clinical experience with FD patients in a tertiary metabolic bone center and to describe the clinical course, BP treatment regimens and response.

Methods: Electronic records were reviewed and summarized.

Results: Eight patients with FD were followed from 1 to 26 years (mean 11 years). The age at presentation varied greatly (7-60, mean 35). Four patients presented with monoostotic and four with polyostotic disease and none had clinical features compatible with McCune-Albright syndrome. The involved sites were femur (5/8), skull (4/8), tibia (4/8), scapula (1/8), ribs (1/8), fibula (1/8) and pelvis (1/8). All but one patient suffered from pain at the affected site, 3/8 presented with bone deformity and 2/8 sustained fractures of the affected bones. All patients were treated with BPs: clodronate daily, pamidronate biannually and zoledronic acid biannually or yearly. In 5/8 of patients significant pain relief was reported.

Of note, one patient delivered three healthy children while on intravenous aminobisphosphonate treatment (average time between the infusion and conceiving was six month). One patient suffered from osteonecrosis of the jaw, prompting BP discontinuation.

Conclusion: In our cohort, the majority of patients were symptomatic and all were treated with BPs. More than a half experienced pain amelioration as a treatment benefit. Zoledronic acid can be administered less frequently than pamidronate. BPs should be considered in all FD patients, although its role in the prevention of disease progression is difficult to determine.

Long-term efficacy of zoledronic acid in patients with Paget`s disease of bone with respect to previous bisphosphonate treatment.

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Introduction: Paget`s disease (PD) is a chronic metabolic bone disease, characterized by focal areas of increased bone turnover. Zoledronic acid (ZA) is highly effective in inducing disease control. Previous bisphosphonate treatment may be associated with a diminished therapeutic response to ZA.

Objective: To compare the long-term efficacy of ZA between bisphosphonates-naïve PD patients and patients previously treated with oral and/or intravenous bisphosphonates other than ZA.

Methods: Medical records of consecutive PD patients that have been treated with ZA and followed at a single medical center between the years 1992 - 2016 were reviewed for medical, biochemical and imaging data. The patients were divided into 2 groups: patients with previous administration of oral or intravenous bisphosphonates other than ZA (Group A), and patients who were bisphosphonates-naïve (Group B). Data on disease-related variables and serum total alkaline phosphatase (ALP) levels were analyzed and compared between the two groups.

Results: The cohort included 63 PD patients (50.8% male, mean age at diagnosis: 65.1±10.7 years). Groups A and B included 36 and 27 patients, respectively. Thirty patients in Group A (83.3%) were treated with intravenous pamidronate prior to ZA treatment. All patients in Group A had disease reactivation and their treatment was switched to ZA. Serum total ALP significantly decreased in both Groups following ZA treatment. Ten and four patients in Groups A and B, respectively, received additional 1-3 treatments with ZA, most of them due to osteoporosis. All the patients had clinically silent disease at the last follow-up visit. Total serum ALP level was within the normal range in all but one patient from Group A at the end of follow-up of 4.58±1.6 and 4.18±1.6 years after ZA administration, respectively.

Conclusion: ZA is highly effective in PD patients with no apparent impact of previous bisphosphonate administration on therapeutic efficacy. ZA maintains long-term clinical remission and normalizes total serum AP levels in nearly all PD patients.

Trabecular bone score uncovers osteopenia and osteoporosis in a large fraction of patients with the metabolic syndrome

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Background: The metabolic syndrome (MetS) is a constellation of medical conditions consisting of central obesity, hyperglycemia, hypertension, and dyslipidemia, in which each acts on bone tissue in different ways. Since MetS often precedes diabetes mellitus (DM), bone fragility might be under-estimated by bone mineral density (BMD) alone. The trabecular bone score (TBS) is a recently introduced non-invasive tool which indirectly assesses bone quality and fracture risk independently of BMD**.**

Aim: To assess the added value of TBS in subjects with the MetS.

Subjects and methods: A retrospective cross-sectional study 104 Caucasian subjects diagnosed with the MetS using the ATPIII criteria. Body composition and bone density were assessed by dual X-ray absorptiometry (GE Lunar Prodigy) and the lumbar spine images were also analyzed using the TBS iNsight (version 2.1.2, Med-Imaps) in order to generate TBS-adjusted T-scores.

Results: The study group consisted of 57 men (55%) and 47 women (45%) with a mean age of 58 ±10 (±SD) and a mean BMI 32.9 ±4.4. The mean T-score was +0.05±1.3 while the mean TBS adjusted T-score was -0.8±1.4. Classified by lumbar BMD T-score, bone density was normal in 83 subjects (80%) but indicative of osteopenia in 19 (18%) and osteoporosis in 2 (2%) participants. After TBS adjustment, however, the number of subjects with abnormal T-score more than doubled to 43%, out of which 29 (28%) were classified as osteopenic and 16 (15%) were clearly within the osteoporosis range. Indeed, most osteoprotic subjects (14/16) were missed by standard BMD but identified by TBS-adjusted BMD. Notably, after TBS adjustment 31% of subjects originally defined as "normal" by BMD alone, had to be reclassified as osteopenic, and 6 % as osteoporotic. Likewise, 32% of BMD-defined osteopenic subjects were reclassified as osteoporotic after TBS adjustment. Subjects reclassified as osteoporotic were significantly heavier (105 kg±5.5 versus 93kg±1.7 p=0.015). Men were more likely to be reclassified than women but this was not statistically significant, the age of the subjects reclassified was not significantly different either.

Conclusions: In this sample of metabolic syndrome patients, bone mineral density identified only one of 7-8 subjects at risk for fragility fractures. In this setting, the assessed bone status is significantly shifted downwards following TBS-adjustment. Hence, the trabecular bone score seems to provide added value over BMD alone in assessing bone fragility in metabolic patients.

Vertebral Fractures in Israeli Patients following Denosumab Discontinuation

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Denosumab (DMAB) efficacy for treatment of osteoporosis was demonstrated in a pivotal trial with a reduction in vertebral and hip fractures compared to placebo during three years and an increment of bone mineral density in a 10 years extension. DMAB causes potent yet reversible inhibition of bone resorption. Bone density declines rapidly upon discontinuation and bone turnover markers increase above baseline in a "rebound" fashion. Spontaneous multiple vertebral fractures after DMAB discontinuation were recently reported. Prior treatment with bisphosphonates (BP) was thought to decrease the risk for this alarming phenomenon. We aimed to describe Israeli experience with a similar clinical scenario.

Methods: A phone survey of physicians engaged in bone metabolism from nine hospitals in Israel was performed. Clinical data of the patients presenting with vertebral fractures upon DMAB discontinuation was summarized.

Results: Five female patients were identified. The mean age was 72±4.9. Three switched to DMAB from BP, the mean exposure was 7.3±3.8 years. One patient received DMAB as a third line, after BP for 4 years and teriparatide for 2 years and one patient as a first line treatment. All but one sustained osteoporotic fractures prior to DMAB initiation. The mean treatment duration was 2.5 years. The reasons for discontinuation were: physician decision (2), administrative (1) and non-osteoporosis related medical condition (2). The fractures occurred 6.4±5.2 month after the missed DMAB injection. 19 vertebral fractures were identified in five patients; all but one presented with multiple fractures, and most were spontaneous.

Discussion: In line with the previous reports, the timing and severity of the fractures raise concern of DMAB discontinuation effect, even in patients with prior prolonged BP exposure. The non-systematic means of data collection, small number and lack of bone turnover markers data make it difficult to conclude causality or mechanism. Doctors, patients and regulatory authorities should be educated about the possible risk of DMAB treatment interruption. Another antiresorptive treatment should be considered if the discontinuation is mandatory

Correlation of distal radius bone density with fracture risk determined by WHO fracture risk assessment model (FRAX)

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Bone mineral density (BMD) evaluation by dual-energy x-ray absorptiometry (DXA) is a mainstay of osteopororosis diagnosis. Lumbar spine and hip are compulsory, while distal radius (DR) DXA is optional. Yet, most fractures occur among patients with osteopenia. To overcome this gap, FRAX was developed. It combines clinical risk factors with BMD and calculates fracture probability. The implementation of FRAX was meant to improve decision making but the model is underused. Occasionally, an osteoporosis is observed only at the DR, resulting in a misdiagnosis when only hip and spine scans are performed. Its incorporation into BMD measurements may guide the physician to initiate pharmacotherapy for fracture prevention.

Our goal was to analyze the predictive value of DR BMD and its correlation with FRAX score.

Methods: Patients undergoing routine BMD measurements were enrolled. Spine, hip and DR were measured. The patients completed a questionnaire regarding risk factors relevant to the FRAX. The FRAX scores for hip and major osteoporotic fractures (MOF) were calculated. Correlation of DR bone density with FRAX scores was tested.

Results: 208 patients (27% men) were included (mean age 66$\pm$11 years). Hip fracture and MOF FRAX scores correlated with DR bone density with Pearson coefficients -0.46 and -0.51, respectively. FRAX hip scores in the lowest versus the highest quartile of DR BMD were 7.7$\pm$6.7 and 2.0$\pm$3.6, respectively (p0.01). In a subgroup of patients with osteopenia of the spine or hip and osteoporosis in DR, mean FRAX score for hip fracture was 6.9%.

Conclusions: DR bone density correlates well with FRAX osteoporotic fracture risk. In a subgroup of osteopenic patients by traditional measurements and osteoporotic by DR scan the FRAX score for hip fractures was impressively high. This subgroup may benefit from DR measurement thus increasing the likelihood of referring physicians to prescribe and the regulatory body to approve an anti-osteoporosis medication. These results are especially important in view of the decline trend in osteoporosis treatment.

Fracture risk assessment with FRAX: validation using real-world data

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Objective: To evaluate the predictive value of FRAX using real-world community data.

Methods: A retrospective population-based cohort including all adult female members of a large Israeli healthcare services provider and insurer. FRAX scores at index (2004) were calculated using computerized health records, and compared to actual incident major osteoporotic fractures (MOF) during the following 10 years.

Results: A total of 141,320 women were eligible, at a median (IQR) age of 58 (54-67) years old, with 13.5% and 2.9% observed vs. 6.9% and 2.2% expected MOF and hip fractures, respectively. The area under receiver-operating characteristic curve (AUC) of FRAX without BMD was 0.65 (95% CI: 0.65, 0.66) for MOF and 0.82 (95% CI: 0.81, 0.82) for hip fracture. A total of 16,578 subjects had BMD data at index, and their risk estimates based solely on BMD exhibited lower predictive performance for MOF (AUC=0.62 vs. 0.65, p-value=0.003) as well as hip fractures (AUC=0.78 vs. 0.84, p-value0.001) as compared with FRAX.

Conclusions: FRAX using electronic health records provides reasonable discrimination despite some underestimation of the absolute risk of non-hip fractures. Integration with routine clinical systems could increase implementation in daily practice and improve risk detection, especially for patients without BMD.

Soroka Fracture Liaison Service (FLS) – rates of mortality and second hip fracture

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Background

Osteoporotic hip fractures are a growing medical and financial burden with increased mortality (15-25%) and recurrent fractures in the year following the hip fracture. A multidisciplinary fracture liaison service (FLS) has been shown to increase anti-osteoportic treatment rates, decrease recurrent fractures and to be cost effective. Furthermore, treatment with IV Zoledronice acid following hip fracture has been shown to decrease mortality by 28% and recurrent fracture by 35%.

Methods

Patients over age 50 admitted to Soroka University Medical Center (SUMC) with hip fracture were offered investigation follow up and treatment by the FLS. Patients were offered an endocrinologist consultation and recommendation on treatment with anti-osteoporotic medication. The aim of this study is to assess the rates of mortality and recurrent hip fracture after the implementation of FLS at SUMC.

Results

As of October 2016, 917 patients were admitted with hip fracture to SUMC, of whom 608 joined the project; mean age 79.14±9.9, 73.9% females, median follow up 10 months (Q1;Q3, 4;18). Patients who died within 30 days of fracture were excluded from analysis (n=30). Rate of mortality was 14.64% (n=89; CI95% 11.92-17.7%) and second hip fracture 3.29% (n=20, CI95% 2.02-5.03). Rates of mortality and second hip fracture according to treatment group were 5.3% and 2.3% for Zoledronic acid (n=131) 10.7% and 3.6% for oral bisphosphonates (n=140), 11.1%, and 9.7% for Denusomab (n=72) and 0% and 16.6% for Teriparatide (n=12).

Conclusions

Medical treatment following hip fracture implemented as part of an organizational FLS has been shown to lead to mortality and repeat hip fractures rates that are similar to what has been reported in the literature in a large clinical trial with zoledronic acid when administered following hip fracture. Long term follow up is needed to confirm the beneficial effects of FLS on mortality and recurrent fractures.

Patients knowledge and opinions regarding osteoporosis, osteoporotic treatment and oral health

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Background: Osteonecrosis of jaw (ONJ), a rare side-effect of antiresorptive treatment, occurs in 0.01% osteoporosis patients, especially after invasive dental procedures. Although evidence is lacking, some professional societies recommend patients undergoing such procedures to interrupt antiresorptive treatment. Media reports related to ONJ and lack of knowledge and mis-information provoke anxiety, and might lead to premature drug interruption. We assessed patients` knowledge and opinions about the association between osteoporosis, its treatment, and oral health.

Methods: Osteopenia and osteoporosis patients attending an outpatient endocrine clinic completed anonymous questionnaires, including socio-demographics; internet use; osteoporosis and oral hygiene status; and 11 questions about the effects of osteoporosis and its treatment on oral health, dental procedures and possible interactions.

Results: 144 patients (67.9±15.5 years, 92% female) were included. 66.2% had 12 years of education, 60.7% were native Hebrew speakers and 52.7% had daily internet exposure. 88% attended the clinic for osteoporosis, and one-third had a previous osteoporotic fracture. 76% were actively taking antiresorptives. 77.2% visited the dentist in the last year and 49.3% underwent a procedure, half of which were invasive. Participants demonstrated poor knowledge regarding associations between osteoporosis, its pharmacotherapy and oral health; 52% did not know whether osteoporosis and oral health were associated and one-third thought osteoporosis could harm the oral cavity. 45% did not know whether osteoporosis treatment could damage fillings or implants and 17% thought it could. 68% wanted to learn more about the subject. Knowledge among patients with/without previous fracture, different education levels and different ethnic backgrounds were similar.

Conclusions: Outpatients with osteoporosis and osteopenia lack knowledge about associations between the disease, its treatment and oral health. Increasing knowledge can improve adherence to osteoporosis treatment and help prioritizing treatments. The medical community should help patients obtain accurate and balanced information.

Virtual Orthopedic-Rehabilitation-Metabolic Collaborative Management for Osteoporotic Hip Fracture

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Purpose: Osteoporosis treatment for hip fracture patients can reduce the risk of additional fractures; yet, most post-fracture patients do not receive it. We reported that multi-disciplinary team management increased osteoporosis treatment rates; however, only 50% of hip fracture patients came to the metabolic clinic for evaluation. To improve adherence, we conducted a prospective "closed-loop" virtual collaborative study where patients were evaluated without formal clinic visits.

Methods: An Orthopedic-Rehabilitation-Metabolic hip fracture team was established. Interventions included vitamin D loading in the orthopedic and rehabilitation departments and individualized osteoporosis treatment. Osteoporosis drug recommendations were approved by the HMO administration and relayed to the family physician. Primary endpoint was drugs issued to patients. Secondary endpoints were vitamin D measurement in the orthopedic and rehabilitation departments, vitamin D levels 65 nmol/l in rehabilitation, and osteoporosis diagnosis and metabolic clinic referral in discharge letters.

Results: Two hundred-six hip fracture patients (81±12.2 years-of-age, 69.5% women) were operated April-September 2016; 154 (74%) were excluded because they were not HMO members, had pathologic or high-energy fractures, died peri-operatively or had post-loading vitamin D level 65 nmol/l. Treatment was recommended for 52 (25.2%) patients: 7 were declined for administrative reasons, 3 died before treatment was administered and 13 of 42 prescriptions (30%) were filled. Zoledronic acid, teriparatide and denosumab injections were recommended to 67%, 19% and 13% of patients, respectively. Vitamin D was measured in 78% in the orthopedics and 82% in rehabilitation departments. Orthopedic discharge letter included osteoporosis diagnosis in 73% and metabolic clinic referral in 91%.

Conclusions: Virtual Orthopedic-Rehabilitation-Metabolic collaboration led to disappointing results, as 30% of recommended prescriptions were issued. Further research is required to remove barriers to osteoporosis care for hip fracture patients, such as providing drug therapy directly to patients during rehabilitation.

The Use of Clinical Data Repository for the Establishment of an Osteoporosis Registry: Epidemiologic Findings

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Background and Objectives: Osteoporosis is a growing public health concern worldwide due to its rising prevalence, excess morbidity and mortality, yet local estimates of its burden in Israel were lacking. We aimed to design, develop and validate an infrastructure which will detect osteoporosis patients in the community.

Methods: An automated registry was built using Maccabi Healthcare Services central computerized health records database, and included patients with at least 2 osteoporosis diagnoses, history of typical low trauma fractures, 2 purchases of relevant medications, or osteoporotic bone density as measured by Assuta centers. The latter was facilitated by employing an Optical Character Recognition (OCR) technology, to extract numeric tables from 250,000 historical PDF reports (2006-2014), as well as by ongoing coded transmission directly from the densitometers to Maccabi database (as of 2014). Automated alerts were constructed for secondary prevention of fractures and monitoring of therapy duration and quality.

Results: A total of 124,000 osteoporosis patients were identified (99,000 currently active), with a point prevalence of 19% in 2014 among members aged 50+, and approximately 7,000 incident cases a year. A third of the identified patients were treatment- naïve. Eight different osteoporosis studies were conducted, revealing among the rest that non-adherence was associated with 13% higher medical costs and 50% increased fracture risk among the elderly (75+), and that physicians' involvement in conveying the importance of therapy was sub-optimal.

Conclusions: This large automated registry can be used both for epidemiology research, safety and efficacy of pharmacologic interventions, outcomes research, as well as real-time identification of under-treated high risk populations leading to improved quality of care.

Fever and hypocalcemia following in hospital osteoporosis treatments: The Soroka FLS experience

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Background

Osteoporotic hip fractures are a growing medical and financial burden in the elderly. Parenteral treatment with IV Zolendrnic acid (ZA) or SC Denosumab are first line treatment options flowing hip fracture in Israel. Both medications have side effects including transient fever and hypocalcemia. Our aim was to investigate the incidence of fever and hypocalcemia following in hospital treatment with ZA or Denosumab in patients with an osteoporotic hip fracture as part of the fracture liaison service (FLS) at Soroka University Medical Center (SUMC).

Methods

As of July 2014, patients over age 50 admitted to SUMC with hip fracture were offered investigation follow up and treatment by the FLS. Patients who were transferred to rehabilitation at the Geriatrics department received an endocrine assessment and received in hospital treatment with par-enteral anti osteoporotic medication after correction of vitamin D deficiency and calcium supplementation Drug choice was based on previous anti osteoporotic treatment and kidney function. Daily body temperature and serum levels of albumin corrected calcium when available, were documented before and after drug administration.

Results

153 patients were hospitalized for rehabilitation in the geriatrics department following hip fracture as of October 2016, mean age 81.53±7.59 years and 75.3% females. 85 patients received IV ZA following paracetamol administration.26 received SC Denosumab. Mean body temperature on the day prior to treatment, day of treatment and the day following treatment with ZA, was 36.86±0.32, 36.87±0.3 and 37.11±0.65 respectively and 36.78±0.3, 36.85±0.33 and 36.82±0.29 with SC Denosumab. Serum albumin corrected Calcium levels decreased from a mean of 9.53±0.51 mg% one day prior treatment to a nadir of 8.82±0.61 3-10 days following ZA.Not enough data was available for the Denosumab treated group.

Conclusions

IV ZA treatment in the first few weeks following hip fracture may cause mild body temperature elevation and mild hypocalcemia.

Resistant Prolactinomas: A Chort of 17 Israeli Patients

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Introduction

Prolactin secreting tumors are the most common pituitary adenomas. Prolactinomas cause hormonal disturbances in women and males, and also mass effects if the adenomas are large enough. These tumors usually respond to treatment with dopamine agonists (DA).

Aims and Methods

We have identified 17 patients (12 males) in two medical centers, diagnosed between 1993-2015 with resistant prolactinomas, defined as prolactin levels above 3 times the upper limit of normal (ULN) or adenoma growth despite a weekly dose of 2 mg of cabergoline.

Results

Mean age at diagnosis was 28±12 (15-55). Fourteen patients had macroadenomas, 2 had giant tumors (40 mm), and one microadenoma; 14 were invasive and 8 patients had visual field deficits. Mean baseline prolactin was 420±765 X ULN (range, 5-2870). At diagnosis 8 of 12 males presented with hypogonadism, and all females had amenorrhea. Mean maximal weekly cabergoline dose was 4±2.2 mg (range, 2-10.5). With DA treatment adenoma size decreased significantly in 12/ 17 subjects. Mean minimal prolactin level on DA decreased to 20±41 X ULN (median, 6), and 7 of 8 patients with visual damage improved. Eight patients experienced loss of initial DA effect. Ten patients underwent trans-sphenoidal surgery, mostly due to lack of response to DA treatment, but only 3 have normalized prolactin. Three patients, received radiotherapy following surgery. Currently, 3 patients normalized prolactin, and 5 others have prolactin below 3 X ULN. Testosterone was not normalized in any male presenting with hypogonadism.

Conclusions

Resistant prolactinomas are uncommon, and usually require multi-modal treatment strategy. In our cohort we were able to control 8 of 17 resistant tumors.

The importance of cannulated prolactin testing as part of the investigation of hyperprolactinemia

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Hyperprolactinemia may be caused by physiological and pathological conditions such as pregnancy, emotional-stress, hypothyroidism, pituitary tumors, among others. In order to differentiate between stress-related prolactin elevation and true elevation, a rest-prolactin-test (RPT) has been part of the evaluation of hyperprolactinemia in many centers. In this test repeated prolactin measurements are drawn from an IV-inserted cannula without repeated venipuncture. According to the American=Endocrine-Society guidelines (2011), a single measurement of elevated serum prolactin, obtained without significant venipuncture-stress, is sufficient for further evaluation. These guidelines make the 'RPT' unnecessary.

Aim: To determine the number of patients with hyperprolactinemia who normalized prolactin-levels during the RPT.

Methods: A retrospective cohort study of patients who underwent a RPT between 2000-2015 in clalit-health-services, Jerusalem.

Prolactin-levels were drown at time 0, 60' and 90' from an indwelling catheter insertion. Patients with abnormal liver or renal functions, elevated TSH, prescribed drugs known to elevate prolactin and woman using OCPs were excluded. Results were analyzed according to the standard values for gender at the time of the test. Prolactin values were transformed to "standardized-prolactin" which is the result of the measured prolactin divided by the upper normal limit (UNL).

Results: 1,026 patients underwent the test. After exclusion criteria, 820 were included with 691 females. Repeated prolactin was normal in 351 patients either before or on time 'zero' of the RPT. Among the 375 with elevated prolactin at time 0, 28% normalized during the 60/90 minutes of the test. Standardized-prolactin values at time 'zero' in the group that normalized the prolactin were significantly lower than in the group that didn't . Median values 1.19 (1.1,1.44)Vs. 2.09(1.59, 2.91) respectively ($P<0.001$).

Higher prolactin at time 'zero' were less likely to normalize during the test. 69.4% of patients with prolactin 1.15-1.3 UNL, normalized during the test, whereas 22.2% normalized with an initial prolactin 1.6-1.75 times the ULN. 97.4% of those with prolactin 2.3 times the UNL didn't normalize.

Conclusion: In our study, 43% of patients normalized their prolactin-levels on a repeated measurement or at time 'zero' of the 'rest-prolactin-test'. Moreover, in those with elevated prolactin at time 'zero', 28% normalized during the RPT . We recommend a repeated prolactin measurement and a 'rest-prolactin-test' in patients with prolactin levels up to twice the UNL in order to avoid unnecessary investigations.

Preparation, characterization and in vitro evaluation of non-pegylated and pegylated chicken and human prolactins

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Introduction: PEGylation has been widely used as a post-production modification for improving biological efficiency *in vivo* due to prolonged half-life in circulation. However, separation of PEGylated proteins is challenging because PEG itself is a relatively inert, neutral, hydrophilic polymer. Although PEGylation affects protein hydrophobicity, Hydrophobic Interaction Chromatography (HIC) has not been extensively applied for the separation of pegylated proteins.

Aim: The aim of the study was to prepare pure PEGylated chicken and human prolactins (chPRL and hPRL), using HIC and testing *in vitro* their biological activity.

Methods: Aliquots of 30 to 80 mg of purified chPRL or hPRL were incubated with a 12-fold molar excess of 20 kDa of methoxy PEG-propionylaldehyde. Prolactins were dissolved in 1M NaH_2PO_4 buffer, pH 6.5; then 1M $NaBH_3CN$ was added, and the dissolved protein was conjugated with PEG. The solution was stirred overnight, dialysed against 50 mM NaH_2PO_4, pH 6.5, and applied onto Phenyl sepharose column pre-equilibrated with 50 mM NaH_2PO_4 with 0.8M ammonium sulfate, pH 6.5. The pegylated proteins were eluted in 50 mM NaH_2PO_4, pH 6.5, containing 0.4 and 0.2 or 0 M $(NH_4)_2SO_4$. Fractions containing the mono-pegylated protein as determined by gel filtration on analytical Superdex-200 column were pooled, dialyzed against $NaHCO_3$ and lyophilized. In competitive binding experiments, the biotinylated hPRL served as a ligand to be competed off by the respective non- or pegylated PRLs. The bioactivities of non-pegylated and pegylated PRLs, were tested in Baf3/rbPRLR and NB2 cell lines.

Results: The monoPEGylated prolactins were eluted with 0.2 or 0M $(NH_4)_2SO_4$. Their respective *in vitro* potency was 12-fold lower as determined in binding and cell bioassays, but their *in vivo* activity is expected to be higher.

Conclusion: The purity of monoPEGylated prolactins is comparable to that obtained by using SEC. This process represents a viable method for purification of PEGylated proteins.

Somatostatin receptors in pancreatic adenocarcinoma: a novel therapeutic target

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Background: Somatostatin (SST) is a hormone involved in regulation of cell growth and apoptosis, *which acts via* five GPCRs (SSTR1–5). Activation of SSTRs can control cell growth by modulating different signaling pathways, including adenylyl cyclase. Recent *in vitro* data suggest the ability of various SSTRs to mediate growth inhibition of pancreatic adenocarcinoma (PDAC). Therefore, effective activation of SSTRs is an attractive therapeutic strategy for PDAC inhibition.

Aim: To assess SSTRs expression pattern in PDAC and study whether these receptors can be effective targets for PDAC inhibition.

Methods: SSTRs expression pattern in PDAC samples (n=93) was evaluated using IHC. PDAC cell lines used Colo-357, MIA-PaCa2 and Panc1. Cell viability was assessed using colony formation assay. cAMP level was assessed using reporter gene system.

Results: SSTR2 and SSTR4 were overexpressed in the vast majority of PDAC clinical samples. Overexpression of all SSTRs except SSTR2 inhibited PDAC cell proliferation. SSTR-5 silencing increased Panc1 colony formation whereas SSTR-2 silencing decreased it. These results suggest that development of an SST analog with high specificity to SSTR3-5 may be of clinical significance to PDAC patients. We developed four novel SST analogs, PTR 86-89, and tested their activity and binding properties in HEK-293 overexpressing each of the SSTRs. Our results show that PTR-86 exhibits the highest affinity towards SSTR3-5. Next, we found that PTR-86 inhibited cAMP accumulation in SSTR3-5 transfected cells, implying the functionality of the analog.

Conclusion: We show that SSTR1 and SSTR3-5 expression is associated with decreased PDAC proliferation. We also show, for the first time, high expression of SSTR4 in the majority of PDAC samples, emphasizing the need for analogs with high binding affinity to SSTR4 in order to serve as a novel treatment for this cancer. The binding and activity properties of PTR-86 make it an excellent candidate for further studies.

unique case of famillial pheochromocytoma presenting with severe end organ damage

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Pheochromocytoma and paraganglioma (PPGL) are rare catecholamine-secreting tumors occurring in less than 0.2 percent of patients with hypertension. Most PPGL are sporadic, however, approximately 30% are part of a familial disorder transmitted in an autosomal dominant fashion

The symptoms and signs in PPGL may include hypertension, tachycardia and headaches but rarely may present with end organ damage.

R.S, a 41 year old male, was admitted to our hospital with severe diffuse abdominal pain, headache and vomiting. Physical examination showed pulse of 130 bpm, blood pressure of 220/140 and mild right upper quadrant abdominal tenderness. Abdominal x-ray showed a distended loop of large intestine. Chest x-ray showed mild congestion. ECG showed sinus tachycardia- 136bpm without signs of ischemia. Laboratory assessment included: mild pre-renal azotemia, mildly elevated hepatocellular and cholestatic liver enzymes, leukocytosis with prominent neutrophilia and markedly elevated troponin I- 790 ng/l (N14). The patient was admitted to ICCU with a working diagnosis of dissecting aorta. An Angio CT was preformed which ruled out the diagnosis but, bilateral prominent adrenal masses (rt-5X6cm lt-2X3cm) and signs of intestinal ileus was found. 24 hour catecholamine and metanephrine urine collection were prominently elevated (X20-100 above normal) and the diagnosis of bilateral Pheochromocytoma was made. Cardiac echo showed diffuse severe left side hypokinesis. Treatment with alfa and beta blockers was initiated with resolution of Takatubu like syndrome. A thorough anamnesis discovered an already known familial RET mutation in codon 618.

We present a unique case of a 41 year old male without past medical history or medications who presented with abdominal ileus malignant HTN and severe end organ damage including takatubu like syndrome turned out to be bilateral Pheochromocytoma as part of a multiple endocrine neoplasm type 2A.

Phaeochromocytoma-paraganglioma (PPGL): Post-operative hypotension is a vanishing phenomenon.

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Background: Persistent postoperative hypotension in pheochromocytoma (PPGL) comprises a serious complication which reportedly occurs in 30-60% of the patients. This phenomenon reflects 1) high doses of antihypertensive drugs; 2) low intravascular volume secondary to chronic catecholamines-induced vasoconstriction with pressure natriuresis; 3) the sudden drop in circulating catecholamines after surgery. It has been shown that tumor size and preoperative levels of catecholamines are directly related to need for post-operative requirement for vasopressor agents in the early period after tumor removal.

Methods: We retrospectively reviewed the rate of post-operative hypotension in relation to the efficiency of preoperative pharmacological preparation of 24 consecutive patients with PPGL.

Results: 22 subjects had adrernal lesions and 2 extra-adrenal tumors. Age was 51.6 ±16.4 years; F/M 11/13; tumor size-3.6 ±1.7cm. Total urinary metanepherine were 3.6±1.7 folds the upper limit of the normal range. All patient were treated with α-blockade (phenoxybenzamine-15, mean dose 58.7±35.6mg/day; doxazosin-9; mean dose 7.7±4.7mg/ day along with high sodium diet and IV saline. The length of the preoperative preparation period was 3.6±2.3 weeks.

Within the first 24-48 hours postoperatively no post-operative hypotention (90 mmHg) was recorded. Systolic BP was 117 ±13.6 (range 95-150) with a diastolic BP of 70 ±11 (range 89-46). In contrast, intraoperative hypotention occurred in 33% of the patients; BP surged, mostly during tumor manipulation in 58%. No statistical difference existed between subjects with and without such BP rises/falls in terms of pre/post- surgical BP or medical treatment, except that higher baseline diastolic BP was linked to intraoperative hypotension.

Conclusion: Contrasting older literature and previous reports, the patients in our cohort did not experience postoperative hypotension. This is most likely due to tight BP control avoiding pre-operative hypotension and adequate volume control. We propose that proper preoperative management in the modern era can drastically minimize post-operative hypotension.

A single center experience treating Neuroendocrine Tumors during 2005-2015: The lung NET subfamily, clinico-pathological characteristics and disease outcome.

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Introduction: The term APUDOMA was first used in 1969 to describe an ACTH producing MTC. It encompasses a group of tumors deriving from neuroendocrine cells present in many organs, from the pituitary to the rectum. Over the last two decades there was an impressive development of this field, known now as Neuroendocrine Tumors (NETs). **Aims**: We aim to summarize the last decade experience of our multidisciplinary team dedicated to treat NETs patients. **Methods:** Following approval of our institutional ethical board, the pathology and clinical records of all NET patients diagnosed and treated at our institution during 2005-2015 were reviewed. MTC, pheochromocytomas, paragangliomas and pituitary tumors were excluded. **Results:** A total of 273 NET patients were identified of which 129 originated in the lungs and 109 in the GEP system. Other NETs not included in this study were: urogenital (8), tumorlets (3), goblet cells (3), MANEC (13), breast and soft tissue (5) and unknown primary (4). After excluding 5 large cell or poor differentiated types, 124 lung NETs were included in this analysis: 37 carcinoid (23 typical, 14 atypical) and 87 small cell carcinoma (SCC). Their respective characteristics were: mean age 54, 57 and 65 years; males 56, 57 and 73 %; smokers 50, 27 and 98 %; primary size 19, 23 and 46 mm; Ki67score 4, 16 and 86%; LNM/DM 12/0, 37/16 and 75/85 %. Overall, 81 out of 124 patients (65%) died during the study period. At a median follow-up of 36, 24 and 12 months, death was observed in 3, 4 and 74 patients with a diagnosis-death interval of 43, 25 and 10 months; for typical, atypical and SCC respectively. While most SCC died from the disease, none of carcinoid patient`s deaths were disease related. Overall survival at last visit was 87, 72 and 15 % for typical, atypical and SCC; respectively **Conclusions:** Compared to SCC, lung carcinoids show a favorable prognosis as expected from other low grade NET tumors. Efforts should focused on new treatment modalities to improve SCC survival

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs): clinico-pathological characteristics and disease outcome of 110 patients treated at single referral medical center in Israel.

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Introduction: GEP-NETs incidence increased markedly over the past decades probably due to increased imaging. GEP-NETs are generally indolent but often have unpredictable biological behavior and aggressive clinical course. **Aims**: To collect information regarding demographics, presentation, pathology characteristics, treatment and outcome of GEP-NETs. **Methods:** Following approval of our institutional ethical board, pathology and clinical records of all GEP-NETs patients diagnosed and treated at our institution during 2005-2015 were reviewed. **Results:** We identified 110 patients with GEP-NETs distributed by site as pancreatic 32 (F=45.1%, age 61.2±6.8), gastric 19 (F=50%, age 66.2±11), duodenum 9 (F=33.3%, age 66.3±12), small bowel 13 (F=25%, age 60±12), appendix 34 (F=55.8%, age 36±19) and colorectal 3. The **pNETs** presented with abdominal pain (45.1%) incidentally (25.8%) or syndromatic (21.8%); including 2 insulinomas, 1 gastrinoma and 4 MEN1 patients. Mean size was 31±23 mm and grading was G1 39.2%, G2 42.8%, G3 17.8%. Distant metastases (DM) were seen in 5 patients (M1=3). Surgery was performed in 61.3%, additional treatment given to 32.2% (re-op, somatostatin analogue, TKI, chemotherapy). The **gNETs** presented mostly during work-up for anemia or GI bleeding (70.6%). Mean size was 15 mm and the majority (82.3%) were GCT1 and there were no DM. The **dNETs** presented with anemia (43%), abdominal pain (43%) or incidentally. None was syndromatic. Mean size was 11.2 mm, 50% were G1, and 2 had DM at presentation. Surgery was performed in 33.3% patients. The **sbNETs** presented with bowel obstruction (27%), abdominal pain (36%) or incidentally. None were syndromatic. Only 15% were G1, 6 had DM (M1=5), and 77% had surgery. Excluding aNETs, the overall mortality at last visit was 23.7% (7.9% disease related) at mean follow-up of 34.5 months. **Conclusion:** GEP-NETs are associated with significant morbidity and mortality. The primary site of the tumor has clinical implication for disease management.

Central diabetes insipidus as early presentation of Erdheim-Chester disease

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Background

Erdheim-Chester disease is a rare form of non-Langerhans cell histiocytosis .This disorder involves mainly long bones but multiple organs and tissues are frequently affected leading to potentially life threatening complications.

Case presentation

We describe a 32 yr. old patient .He was diagnosed with central DI in 2008. MRI performed in 06/2008 disclosed the lack of posterior pituitary ***bright spot***. In 2010 he developed secondary hypogonadism without other anterior pituitary hormone deficiencies. Another MRI was performed and thickened nodular pituitary stalk with elliptic lesion 6x6x6 mm was found. To exclude sarcoidosis and other systemic disease, he underwent CT of chest and abdomen. .Because of high level of serum AFP, CSF was examined and discloses normal AFP and HCG levels. Since 2014 he starts suffering from severe pain in ankles and knees. Bone scan was performed and intense symmetric uptake was found in the elbows and lower extremities. BM biopsy was normal . In 12/2015 the patient was hospitalized for severe abdominal pain in the right flank. The abdominal CT showed fatty inflammation of mesenteric lymph nodes and perinephric space compatible with mesenteric panniculitis, confirmed by explorative laparoscopy. New osteosclerotic lesion was found in the right iliac bone on CT. In 02/2016 he was again admitted because of severe ankle pain. The bone scan showed intensive homogenous uptake in the limbs. A presumptive diagnosis of Erdheim-Chester disease was made. It was confirmed by bone marrow biopsy from left tibia. BRAF V600E mutation was not found. Treatment with interferon was started.

Conclusion.

We presented the case of a very rare disease . Although the patient presented as apparently idiopathic DI, the clinical course over time remember us that infiltrative disorders are a possible cause of DI and that high level of suspicion is needed to avoid delay in diagnosis and management and to prevent unnecessary medical and surgical procedures

Clinical experience with adrenal venous sampling in differentiating unilateral vs. bilateral primary aldosteronism.

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Introduction: In some cases of primary aldosteronism (PA), adrenal venous sampling (AVS) is considered mandatory to differentiate between unilateral and bilateral adrenal disease, to decide whether a patient will benefit from unilateral adrenalectomy. However, mainly due to technical difficulties and lack of experience in AVS among angiographers, it is not commonly performed.

Aim: To share our experience with AVS, hoping to expand its use and offer this procedure when required**.**

Methods: We summarize our initial experience with AVS in 5 patients with PA. All patients had screening and confirmatory tests consistent with PA, but with uncertainty regarding surgical treatment benefit. AVS protocol was performed as follows: adrenal veins were sequentially catheterized during continuous ACTH infusion. Successful adrenal vein *catheterization* was confirmed based on selectivity index 5 (adrenal/ peripheral vein cortisol concentration ratio 5). We used lateralization index 4 to identify unilateral disease demanding surgery.

Results: Two patients with positive AVS lateralization were referred to adrenalectomy. In the first case, a 42 y.o. male, following AVS lateralization underwent left adrenalectomy despite harboring right 24 mm adrenal adenoma and only mild left adrenal hyperplasia. Another case is a 55 y.o. patient; with a small 13 mm left adrenal adenoma that corresponded to AVS lateralization. Our reservations whether the patient would benefit from surgery were set after positive AVS lateralization. In both patients after surgery hypokalemia resolved and hypertension significantly improved. Following negative lateralization on AVS, two patients (57 and 62 y.o.) had not been referred to surgery despite harboring 10-15 mm unilateral adrenal adenoma. In a 62 y.o. patient AVS was technically unsuccessful. No complications were observed.

Conclusions: Our experience shows that AVS can be done successfully with no complications and in some cases of PA, the procedure can be offered to guide the appropriate treatment modality.

Ascorbic acid treatment for patients with combined mineralocorticoid and glucocorticoid deficiency secondary to nicotinamide nucleotide transhydrogenase mutation

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Introduction:

Nicotinamide nucleotide transhydrogenase (NNT) mutations were recently found to cause decreased detoxification of reactive oxygen species (ROS) in adrenocortical cells and consequently severe clinical glucocorticoid or combined mineralocorticoid and glucocorticoid deficiencies.

Cultured fibroblasts from patients carrying homozygous NNT mutations have increased levels of ROS and aberrant mitochondrial morphology.

Ascorbic acid, a known antioxidant, and an essential vitamin, has been used in therapeutic trials in several diseases (e.g. cancer, diabetes and cardiovascular diseases) resulting in significant clinical improvement without major adverse effects.

Aim:

This study aimed to assess the effect of ascorbic acid treatment on the ROS levels and mitochondrial morphology in cultured fibroblasts from 3 affected patients homozygous for NNT mutations.

Methods:

Patient and control fibroblasts were maintained in DMEM with or without 10µM L-ascorbic acid. Cell growth was measured using a colorimetric method with Methylene Blue staining. Intracellular ROS production was measured using 2',7'-Dichlorodihydrofluorescein diacetate with normalization to the number of cells.

Mitochondrial morphology was assessed using mitotracker red staining.

Results:

patients` fibroblasts carrying homozygous NNT_ mutations) p.G200S,_p.Y388S) had 23-40% higher ROS levels when compared to control fibroblasts. Administering 10µM L-ascorbic acid decreased ROS levels in the mutated fibroblasts by 12-34%, and actually normalized ROS levels in the mutated fibroblasts.

Furthermore, pre-treatment mitochondrial morphology in mutated cultured fibroblasts revealed that 57-72% of mitochondria were damaged with punctate instead of reticulo-tubular appearance. Ascorbic acid treatment resulted in reduction of the pathological punctate appearance by 16 to 25% in NNT mutated homozygous fibroblasts.

These results indicated in vivo interventional study which is currently conducted.

Conclusion:

Ascorbic acid reduces ROS content and improves mitochondrial morphology in NNT mutated patients` fibroblasts.

Further clinical trials are warranted in order to assess ascorbic acid as a steroid sparing medication in NNT impaired patients.

Characterization of Orthopedia-expressing neurons in the Arcuate Nucleus

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The arcuate nucleus (ARC) located in the mediobasal hypothalamus, plays a key role in regulating energy homeostasis and is composed of several neural populations, which mediate opposing effects on food intake and energy expenditure. Orthopedia (Otp) is a transcription factor involved in the embryonic development of distinct subset of hypothalamic neurons. Otp expression is maintained in the mature hypothalamus of a mouse, yet its expression pattern and its role in the ARC neurons is still unknown. In this study we aim to identify and characterize Otp expressing neurons in the ARC. Otp-expressing neurons were identified using immunohistochemistry (IHC), and the different neural populations were identified using either IHC or ARC-specific reporter mouse lines. Images were captured using a confocal microscope. Quantification of neurons and colocalization was measured using IMARIS software. Our results show differential distribution with orexigenic and anorexigenic neurons, which may suggest a role for Otp in metabolic regulation.

Role of micro-RNAs in Thrombospondin-1 Expression in Bovine Luteal Cells

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Introduction: Our previous studies showed that a feed-forward loop exists between thrombospondin-1 (THBS1), TGFB1, and SERPINE1, where all three genes were induced in the regressing corpus luteum (CL). Their gene products can promote vascular instability, apoptosis, and matrix remodeling during luteolysis. THBS1 reversed FGF2 actions in luteal endothelial and granulosa cells (LEC, LGC) by inhibiting their proliferation and survival. Furthermore, THBS1 was suppressed by FGF2; TGFB1 on the contrary, elevated THBS1 expression. To better understand the mechanisms regulating THBS1 expression we aimed to identify relevant microRNAs (miRs) targeting THBS1 and study their actions in luteal cells.

Methods: TargetScan prediction tool was used to identify candidate miRs. Five miRs conserved in vertebrates were chosen for further investigation (miR-1, miR-18a, miR-144, miR-194 and miR-221). LEC were transfected with miRNA mimics and inhibitors, then mRNA and miRNA levels were determined by quantitative-PCR. Cell viability were estimated with XTT kit.

Results and discussion: Of the five miRs examined, miR-1, miR-194 and miR-221 overexpression significantly decreased THBS1 to levels 60-70% lower than in controls. These three miRs were endogenously expressed in CL, LGC and LEC. MiR-221 was the only miR inversely regulated by FGF2 and TGFB1. FGF2 rapidly upregulated miR-221, before inhibition of THBS1 was detected, while TGFB1 simultaneously increased THBS1 and reduced miR-221. To assure that miR-221 directly targeted THBS1, cells were transfected with anti-miR221. Indeed, anti-miR221 increased THBS1 mRNA; furthermore, it prevented FGF2 from inhibiting THBS1 expression in these cells and further up-regulated THBS1 by TGFB1. Since THBS1 is responsible for the induction of SERPINE1 (via TGFB1), miR-221 was expected to inhibit SERPINE1 which indeed occurred. Consistent with THBS1 inhibition, miR-221 elevated (160%) viable LEC numbers. These finding suggest that miR-221 is regulated in physiologically significant manner; by targeting THBS1 and SERPINE1 it may affect vascular health in the CL.

Interferon tau Inhibits Luteolytic Responsive Genes In Bovine Corpus Luteum.

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Introduction: The establishment of pregnancy in ruminants involves the suppression of the endometrial luteolytic mechanism to maintain corpus luteum (CL) function. Production of interferon tau (IFNt) by the trophoblast disrupts uterine release of luteolytic prostaglandin F2alpha (PGF) pulses. We have shown that to accomplish CL regression, PGF induces in the CL- TGFB1, thrombospondin-1 (THBS1) and plasminogen activator inhibitor-1 (PAI1) that act to curtail angiogenic support, cell survival, and ECM maintenance. IFNt, released into the uterine vein, has potential endocrine action. However, the direct actions of IFNt on CL functions are still debatable.

Aim: To investigate effects of IFNt on luteal slices and luteal endothelial cells (LECs).

Methods: CL slices from mid-cyclic cows and LECs were treated with various concentrations of IFNt. Phospho-STAT1 and THBS1 protein were analyzed by western blotting. Interferon Regulatory Factor-9 (IRF9) and protein inhibitor of activated STAT-1 (PIAS1) were silenced with siRNAs. Viable cell numbers, mRNA were measured by XTT and qPCR, respectively.

Result: IFNt induced phosphorylation of STAT-1 in LECs in a time-dependent manner. In both CL slices and LECs, IFNt elevated STAT1, STAT2, IRF9, PIAS1 and Interferon-stimulated genes (ISGs: MX2, ISG-15 & OAS-1). PIAS1 knockdown in IFNt-stimulated LECs upregulated ISGs. These findings demonstrate that IFNt acts via type-1 pathway in CL. Additionally, IFNt alone induced cell numbers while PIAS1 knockdown abolished this effect, suggesting the importance of PIAS1 in IFNt mediated cell survival. Notably, IFNt significantly down-regulated luteolytic genes otherwise induced by PGF, such as endothelin-1, TGFB1, THBS1 and PAI-1 in LECs, TGFB1, THBS1 and PAI-1 were also inhibited by INFt in CL slices.

Conclusions: These results demonstrate that the CL behaves as a classical target tissue of IFNt. Furthermore, the reduction in luteolytic genes may suggest that anti-luteolytic actions of IFNt are exerted on uterus and CL as well.

Differential Roles of PKC Isoforms (PKCs) and Ca^{2+} in GnRH and Phorbol 12-myristate 13-acetate (PMA) Stimulation of p38MAPK Phosphorylation in Immortalized Gonadotrope Cells

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We examined the role of PKCs and Ca^{2+} in GnRH-stimulated p38MAPK phosphorylation in the gonadotrope derived αT3-1 and LβT2 cell lines. GnRH induced a slow and rapid increase in p38MAPK phosphorylation in αT3-1 and LβT2 cells respectively, while PMA gave a slow response. The use of dominant negatives for PKCs and peptide inhibitors for the receptors for activated C kinase (RACKs), has revealed differential role for PKCα, PKCβII, PKCδ and PKCε in p38MAPK phosphorylation in a ligand- and cell context-dependent manner. The paradoxical findings that PKCs activated by GnRH and PMA play a differential role in p38MAPK phosphorylation may be explained by differential localization of the PKCs. Basal, GnRH- and PMA- stimulation of p38MAPK phosphorylation in aT3-1 cells is mediated by Ca^{2+} influx via voltage-gated Ca^{2+} channels and Ca^{2+} mobilization, while in the differentiated LβT2 gonadotrope cells it is mediated only by Ca^{2+} mobilization. p38MAPK resides in the cell membrane and is relocated to the nucleus by GnRH (~5 min). Thus, we have identified the PKCs and the Ca^{2+} pools involved in GnRH stimulated p38MAPK phosphorylation.

GnRH induces ERK-dependent bleb formation in gonadotrope cells, involving recruitment of members of a GnRH receptor-associated signalosome to the blebs

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

Long-Term Anthropometric Outcome Of Girls With Non-Classical Congenital Adrenal Hyperplasia Diagnosed In Childhood

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Background: Data on anthropometric outcomes in patients with non-classical 21-hydroxylase deficiency (NCCAH) are sparse.

Objectives: To investigate long-term effects of NCCAH on height and weight.

Methods: A retrospective, cross-sectional study of 105 girls with NCCAH aged 8.4±4.1 years (0.4-18), mean follow-up 11.4±7.5 years.

Outcome measures were height, weight and BMI, expressed as standard deviation score (SDS) at diagnosis, compared to last visit and compared to those of their mothers, fathers and siblings. Patients were stratified by pubertal stage at diagnosis: prepubertal, pubertal (tanner 2-4) and fully pubertal.

Results: Mean daily hydrocortisone dose was 11.6±5.4 mg/m^2. At diagnosis, height- , weight- and BMI-SDS were similar to those of parents and siblings; bone age to chronological age ratio was 1.15±0.24. Height-SDS at last visit was significantly lower than that at diagnosis (-1.7±1.4 vs. -0.2±1.3, *P*0.001) and lower than mothers (*P*0.001), fathers (*P*0.001) and sibs (*P*0.002). At admission, Patients that were fully pubertal at diagnosis were significantly shorter than prepubertal and pubertal patients, and shorter compared to prepubertal, at last visit. A significant association was found between lower height-SDS at last visit and longer treatment duration (r= -0.46, *P*0.001) but not with hydrocortisone dose (r=-0.22, *P*=0.07). Current weight-SDS slightly decreased compared to baseline (0.1±1.4 vs. -0.48±1.36, *P*0.001), while BMI-SDS was similar to baseline (0.28±1.31 vs. 0.48±1.1, *P*=0.09). Most recent weight-and BMI-SDS were significantly lower than parental weight-and BMI-SDS. Age at menarche was earlier in affected girls compared to their mothers (12.3±1.3 vs 12.7±1.2 years, *P*0.05).

Conclusions: NCCAH diagnosed in childhood is associated with compromised height. Earlier menarche, longer steroid treatment duration and older age at diagnosis may be risk factors. It is encouraging to see that BMI-SDS did not increase over time, despite hydrocortisone treatment.

Pediatric to Adult Transition Clinic in Endocrinology: Clinical Importance, Adherence to Follow-Up and Patient Satisfaction

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Objective: The importance of pediatric to adult transition clinics for patients with chronic medical problems is well established. A structured transition process is associated with improvement of the medical treatment and better adherence for follow up. However, data regarding the favored model of transition is limited. In Meir Medical Center we conduct an endocrinology transition clinic since September 2014. The transition meetings take place in the adult endocrinology unit in the presence of both the pediatric and the adult endocrinologists, after which the patients are invited for follow up in the adult endocrinology unit.

Methods: A retrospective analysis of the endocrinology transition clinic visits since 1/9/2014 to 31/12/2016 was conducted. Epidemiologic and clinical data was collected from the electronic files. The patients were applied to fill a satisfaction questionnaire 6-30 months after the visit at the transition clinic.

Results: From the 81 patients referred by the pediatric endocrinologist, 70 patients visited the transition clinic in the study period (86.4%). Patients` age was 20.26±2.34 with female predominance (n=63, 90.0%). Most of the patients (n= 67, 95.7%) were unmarried. The most prevalent diagnoses were polycystic ovary syndrome (n=33, 47.1%), Hashimoto`s thyroiditis (n=28, 40.0%) and obesity (n=23, 32.8%). Therapeutic change was recommended in 20 patients (28.6%) and further diagnostic evaluation was suggested in 21 patients (30.0%). The adherence to follow up in the adult endocrinology unit was 80%. Of the 43 patients who filled satisfaction questionnaires, the vast majority were satisfied or highly satisfied from the transition process (13.93% and 81.93%, respectively).

Conclusions: The Meir Medical Center model for transition from pediatric to adult endocrinology clinic has clinical importance and promises high rate of patient satisfaction and adherence to follow up. The implementation and evaluation of this simple model in other areas is suggested.

Effects of a Stressful Environment (SE) on Height, BMI and Menarche

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Background: Children's exposure to stress predicts poor health. Poor growth and maturation are recognized indicators of poor health.

Hypothesis: SE correlates with height, BMI and menarche. We correlated seven indicators of SE with countries' average adult height, BMI and menarche age.

Methods: Data for 57 countries of average men and women's height, BMI and menarche age were collected from WHO report. They were correlated with the countries' score for SE, built on seven indicators (data World Databank and Transparency International): annual homicide rate, GDP per capita, income inequality (Gini coefficient), corruption perception, urban air pollution and life expectancy at birth. PCA clustered the indicators, and we assessed the effects of SE on height, BMI and menarche age by regression analyses.

Results: The SE indicators clustered in two: QOL, including pollution, life expectancy, GDP and corruption, and the Social factor, including homicide and inequality perception. The QOL cluster correlated positively with male (r=0.63; p0.0001) and female height (r=0.55; p0.0001) and with male BMI (r=0.41, p=0.0001), while the female BMI (quad r=0.38, p=0.024) and menarche age showed a U-shape regression (quad R=0.57, p0.0001).The Social cluster correlated negatively with male (r=0.46, p0.0001) and female height (r=0.44, p0.0001) and female but not male BMI (-0.47, p0.0001).

Conclusions: 1. Adult height, as a measure of child's growth, is a strong and BMI a weak indicator of SE. 2. Women's BMI is low and menarche is strongly delayed in the lowest and less so in the highest QOL score countries. 3. The strongest indicator for poor growth is the QOL cluster: pollution, life expectancy, GDP and corruption, followed by the Social factor: homicide and economic inequality.

Long-Term All-Cause Mortality in Thyroid Carcinoma Patients:

A Retrospective Cohort Study

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***Background*:** The association between endogenous subclinical hyperthyroidism and mortality was shown in numerous studies. Iatrogenic subclinical hyperthyroidism is a part of treatment with levothyroxine (LT4) in thyroid carcinoma (TC) patients.

Objective: The assessment of all-cause mortality in TC patients compared to subjects without any thyroid disease.

***Methods*:** We conducted retrospective study with two study groups, aged 18 years and more, evaluated at the period from 01.01.2000 to 30.06.2016, with a review of computerized database of Clalit Health Medical Organization (CHMO), a largest health care organization in Israel. The first study group included TC patients without another previous cancer, the second one included patients without any thyroid disease and without any previous cancers. Cox regression analyses were used for comparison all-cause mortality hazard ratio (HR) between the two study groups.

***Results*:** A total of 29639 patients were followed for a median of 7 years. The TC group included 5677 and the control group included 23962 patients.

After adjustment for age, gender, cerebrovascular and cardiovascular disease, HTN, DM, dyslipidemia and current smoking at the beginning of the follow up, multivariate Cox regression analysis revealed increased mortality in TC patients (HR 1.9 CI 1.71-2.1). The risk of death increased with age 55 and more in the two groups, but was more pronounced in TC patients. Towards the end of the follow up the higher prevalence of HTN (p=0.002), dyslipidemia (p0.001) and cardiovascular disease (p=0.05) was found in TC patients who died (all-cause mortality) compared to the non- TC control cohort group who died within the same time frame.

***Conclusions*:** This large nationwide population study showed high all-cause mortality among individuals with TC than among those without TC. Further study is needed to ascertain the specific causes of death in this high risk group of TC patients.

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