האגודה הישראלית לאנדוקרינולוגיה IES Israel Endocrine Society

The 45th Annual Meeting of the Israel Endocrine Society

April 12-14, 2016, Inbal Jerusalem Hotel

Program & Abstract Book

WELCOME ADDRESS

Dear colleagues;
It gives us great pleasure to welcome you to the 45th Annual Meeting of the Israel Endocrine Society, IES.

This is the last meeting organized by the currently serving Executive Committee, or as we call it in Hebrew, the IES Va'ad. Toward the end of this conference the new Va'ad we have chosen in the past two weeks of elections- will be announced. We heartedly thank the stepping down Va'ad and wish success to the newly elected one.
For the concluding meeting of the serving Va'ad we follow the society's tradition to make a special effort and organize a day longer meeting and choose a unique venue for the event. The Inbal Hotel is our quality choice venue, placed in the heart of Jerusalem, close to the Old City and historical monuments, as well neighboring the lively centers of the city's present life.

As we always try to do, this year the program topics are meant to reflect the latest developments in clinical and basic advancements in endocrinology. To this end we shall enjoy the plenary presentations, attend a plethora of symposia lectures covering "from bench to bedside" topics, have meet-the professor discussions and enjoy the oral and guided posters presentations by our junior stuff and students. We will also have the traditional Prize session to encourage and emphasize excellent research.

We would like to thank our distinguished guests and lecturers from abroad, Philippe Froguel, Rodney Hicks, Robert Jensen, Constantine Stratakis, Anthony Hollenberg, Outi Makitie, Frank Biro, and Karine Rizzoti. We deeply appreciate the receptiveness of our guests from far (Australia, USA, Finland and UK), who kindly accepted our invitation to come in somewhat troubled times and help IES making a statement that life and science must continue undisturbed. We also deeply appreciate the willingness of the local invited speakers (non-IES members) to come and share their wisdom with us and make this conference so inspiring: Adi Mizrahi, Ronit Kochman, Gideon Kopernik, Avraham Ben Chetrit, Gadi Pelled, Zvi Granot, Neta Erez, Carmit Levi, Nissim Benvenisty, Shulamit Levenberg, Ron Piran and Sigal Fishman.

We would like to thank all those who are involved in the organization of this meeting, the Abstract reviewers and the members of the Executive Committee for spending many hours making this conference interesting and enjoyable. We also thank the supporting pharma companies and the dedicated people of Paragon Israel. We look forward to a successful conference.

On behalf of the 2016 Meeting Organizing Committee

Eddy Karnieli	President, Israel Endocrine Society
Yossi Orly	Chair, Program Committee
Yoav Sharoni	Co-Chair Program Committee
Carlos Benbassat	Co-Chair Program Committee

IES EXECUTIVE COMMITTEE

Eddy Karnieli, M.D., President

Nehama Zuckerman-Levin, M.D., Secretary

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תודתנו נתונה לחברות נותנות החסות

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- (CSIRO) Commonwealth Scientific Research Organization 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".

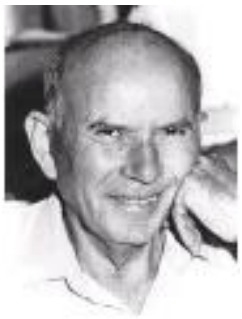
בזכות תכונותיו התרומיות כאינטלקטואל וכמדען, נשא פרופ' לינדנר תפקידים רבים נוספים: הוא מונה במכון ויצמן כדיקן הפקולטה לביולוגיה, לראשות הועדה לקידום מדענים ולוועדה המייעצת של נשיא המכון. בנוסף לכך, הוא היה חבר בחבר הנאמנים של ביה"ח הדסה בירושלים, היה פעיל בהקמת הפקולטה לווטרינריה ואף היה נשיא האגודה הישראלית 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	2002 – משה פיליפ
1990 – מרדכי ליסקוביץ	2003 – שרה פרבר
1991 – ראובן רייך	2004 – פואד פארס
1992 – אבי קרסיק	2006 – איתן גרוס
1993 – רוני זגר	2007 – אילן שמעון
1994 – עירית גרנות	2008 – חגית אדלר-פינקלמן
1995 – אורי פלס	2009 – אסף רודיך
1996 – דורית אהרוני	2010 – גיל ליבוביץ
1997 – חנה קנטי	2011 – אלון חן
1998 – בנימין גלזר	2012 – פיליפה מלמד
1999 – מיכל נאמן	2013 – יובל דור
2000 – רינה מידן	2014- ערן בורנשטיין
2001 – חיים ורנר	2015- איילת ארז

2016- פרופ׳ ערן אלינב

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- ד"ר בני גורפינקל

Preliminary Program

April 12, 2016

16:00-16:30	**Registration & Reception**	
16:30- 17:15	Plenary lecture 1: **Philippe Froguel** (UK) **Chair: Eddy Karnieli** "New Insight into Genetics of Diabetes and Obesity"	
17:15-18:45	**Symposium 1** **Neuroendocrine tumors NET** **Chairs: David Gross, Yodphat Krausz** **Hall A**	17:15-18:15 Ima Ima- **New Basic Concepts** **Chair: Yossi Orly** **Hall B**
	Rodney Hicks, Australia "The Role of Functional Imaging in NET "" Diagnosis, Treatment and Follow-Up	**Adi Mizrahi** (HUJI) "Becoming A Mother - New Smells and Sounds in the Mother's Brain"
	Simona Glasberg (Hadassah) "Update in Clinical Trials in NETs - What's in the Pipeline"	
	Robert Jensen, USA "Gastrinoma - State of the Art"	

April 13, 2016			
07:30-08:30	**Registration, Exhibition Visit, Gathering and Refreshments**		
08:30-10:15	**Oral Presentations** (3 Parallel Sessions)		
	Thyroid **Chairs: Sagit Solotov and Yardena Tenenbaum-Rakover** **Hall A**	**Pediatric Endocrinology** **Chairs:Yael Lebenthal and Dalit Modan** Hall B	**Reproduction** **Chairs: Nava Dekel and Berta Levavi-Sivan** Hall C
10:15-10:45	**Coffee Break and Exhibition Visit**		
10:45- 11:30	Plenary lecture 2: **Constantine Stratakis,** USA **Chair: Yona Greenman** "Update on the Clinical Investigation and Genetics of Cushing Syndrome"		
11:30-12:45	Guided Poster Session		
	Group 1: Diabetes Chairs: Hilla Knobler, Joelle Singer	Group 2: Thyroid, Pediatric, Reproduction Chairs: Zaki Kraiem, Eyal Robenshtok	Group 3: Obesity, Bone, Adrenal Chairs: Yossi Levy, David Zangen
12:45-13:45	**Lunch Break**		
13:45- 14:30	Plenary lecture 3: **Anthony Hollenberg,** USA **Chair: Zaki Kraiem** "New Approaches to the Diagnosis and Treatment of Thyroid Disease"		
14:30-16:00	Symposia 2-3 (parallel)		
Hormone Replacement Therapy HRT **Chair: Zeev Blumenfeld** **Hall A**		**Pediatric Bone** **Chairs: David Strich, Nehama Zuckerman-Levin** **Hall B**	
Ronit Kochman (Hadassah) **"**Updated treatments of the Menopause and beyond"		**Outi Mäkitie**, Finland "Clinical and Genetic Characteristics of Pediatric Osteoporosis"	
Gideon Kopernik "Cardiovascular system- menopause and HRT"		**Hochberg Zeev** (Technion) "Bone maturation and bone age'"	
Avraham Ben Chetrit (SZC) "Menopausal Hormone Therapy for Breast Cancer Survivors"		**Gadi Pelled (**HUJI) Activation of Endogenous Stem Cells: Novel Therapies **"** **"**for Bone Regeneration	
16:00-16:30	**Coffee Break and Exhibition Visit**		
16:30-18:00	Symposia 4-5 (parallel)		
Endocrine Disruptors **Chairs: Karen Tordjman and Naomi Weintrob** **Hall A**		**Tumor Environment** **Chair: Haim Werner** **Hall B**	
Frank Biro, USA "Impact of Yesterday's Genes and Today's (diet and) Chemicals on Tomorrow's Women"		**Zvi Granot** (HUJI) "Neutrophils in Cancer, Old Controversies and New Perspectives"	
Ronit Machtinger (Sheba) "EDCS and Epigenetics"		**Neta Erez** (TAU) "Breaking Bad: Cancer Associated Fibroblasts Are Reprogrammed from Growth Inhibitory to Tumor-Promoting in Breast Cancer"	
Hagai Levine (Hadassah) "EDCs and Male Reproduction"		**Carmit Levy** (TAU) **"**Bi-Directional Communication between Melanoma Cells and the Micro Environment"	
18:00-19:00	Meet the Professor / Expert (2 Parallel Sessions):		
Outi Makitie (Finland) "Update on treatment of pediatric osteoporosis"		**Constantine Stratakis**, USA "Approach to the patient with macronodular adrenal hyperplasia"	
19:00-19:30 **19:30-21:30**	Buffet light dinner הקרנת הסרט "הטנור"- אודות זמר אופרה המתמודד עם סרטן התירואיד. הרצאת פתיחה תנתן ע"י דר' יקי כהן,מנהל מכון השמיעה והדיבור,מרמב"ם בנושא: **"טיפול בהפרעות קול הקשורות לניתוחי בלוטת התריס"**		

April 14, 2016			
07:30-08:30	**Registration and Exhibition Visit**		
08:30-10:15	**Oral presentations** (3 Parallel Sessions)		
	Bones, Adrenals and NET **Chairs: Liana Tripto and Eti Osher** Hall A	**Diabetes and Obesity** **Chairs: Amir Tirosh and Gil Leibowits** Hall B	**Growth/Cancer** **Chairs: Yoav Sharoni and Haim Werner** Hall C
10:15-10:45	**Coffee Break and Exhibition Visit**		
10:45-11:30	**Plenary Lecture 4: Karine Rizzoti,** UK **Chair: Philippa Melamed** **"Stem cells & Pituitary Development"**		
11:30-13:00	Symposia 6-7 (2 Parallel Sessions)		
	Stem Cells at the Pursuit of Translational Biology **Chair: Benjamin Reubinoff** **Hall A**	**Thyroid Cancer** **Chairs: Carlos Benbassat** **Hall B**	
	Nissim Benvenisty (HUJI) "Modeling Human Disorders using Pluripotent Stem Cells"	**Eyal Robenshtok** (Rabin Center) "The 2015 Thyroid Nodule and Cancer Guidelines - What's New?"	
	Shulamit Levenberg (Technion) Adipose Derived Endothelial and Mesenchymal Stem Cells Enhance Vascular Network Formation and Induce Vascularization of Engineered Tissue Flaps	**Anat Jaffe** "Molecular Analysis of Indeterminate Nodules"	
	Ron Piran (BIU Zfat) "PAR2: a Passe-Partout for Regenera-tion, Transdifferentiation, and Death in Diabetes and Much More"	**Liora Lazar** (Schneider) **"**Pediatric Thyroid Cancer"	
13:00-14:00	**Lunch Break**		
14:00-15:45	**Prizes session and General Assembly**		
	Lindner Prize Lecture (30 min) **Chowers Prize Lecture** (15 min) **Prizes for Best Clinical/Basic Abstracts** (15 min) **IES Members Assembly Meeting** (45 min) **ELECTIONS RESULTS**		
15:45-16:00	**Coffee Break and Exhibition Visit**		
16:00-17:30	Symposia 8-9 (2 parallel)		
	Pregnancy Endocrinology **Chair: Yoel Toledano, Ronit Koren** **Hall A**	**Obesity and Metabolism** **Chair: Assaf Rudich** **Hall B**	
	Dania Hirsh (Rabin) : Hyperparathyroidism	**Sigal Fishman** (Sourasky)**:** "GIP - a Linker between the Metabolic and Immunologic Systems"	
	Naomi Weintrob (Sourasky) Management of Congenital Adrenal Hyperplasia During Pregnancy - Optimizing Outcomes	**Amir Tirosh** (Sheba) " The Food Preservative Propionic Acid Induces Post-Prandial Hepatic Insulin Resistance – A Neuroendocrine Mechanism"	
	Yona Greenman (Sourasky) "Pregnancy & Cushing"	**Mogher Khamaisi** (Rambam & Technion) "What is new in diabetic wound treatment: A potential use of human inducible stem cells"	

New Insight into Genetics of Diabetes and Obesity

Philippe Froguel
CNRS-Pasteur Institute-Lille University, Imperial College London, UK and

The heritability of type 2 diabetes and obesity are highest amongst most common diseases (50-90%). However, there are heterogeneous familial disorders: 2-5% of T2D or obese patients suffer from a monogenic condition. In 80% of "atypical" diabetic patients (with no antibodies), a genetic diagnosis is possible, leading in most cases to true personalized medicine at lower cost and more effective than conventional treatments. Indeed, all these patients have a major impairment in insulin secretion. Next Generation Sequencing (NGS) has revolutionized the genetic screening of these patients: targeted NGS focused on the >20 atypical T2D genes is routinely proposed. However, exome sequencing may be now the best option for both genomic medicine and research towards novel diabetes genes. In obesity, up to 30% of severe obesity cases (e.g. in consanguinous populations) are due to single mutations, usually in the leptin-melanocortin pathway.

Common T2D and obesity are polygenic diseases: GWAS have identified >200 loci/genes contributing to diabetes and/or to obesity. There are evidence that most of the T2D loci are involved in beta-cell function but many T2D risk contributing genes are poorly known. Rare variants are also contributing to T2D risk. In obesity, there are uncertainties about the impact of these genes on physiology, which may be not restricted to appetite regulation.

Genetics doesn`t explain all the heritability of diabetes and obesity and epigenetic changes are probably contributing to the development of metabolic disorders and of their complications (e.g. non alcoholic fatty liver disease).

Update in Clinical Trials in NETs - What`s in the Pipeline

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Neuroendocrine tumours (NETs) belong to a heterogeneous family of neoplasms, with a variable clinical behavior; they may be functioning or not functioning, ranging from well-differentiated slow growing neuroendocrine tumours to poorly differentiated neuroendocrine tumours, which are highly aggressive malignant tumours. As the incidence and prevalence of NETs is increasing, the primary treatment goal for patients with NETs is curative, with symptom control and limitation of tumor progression as secondary goals. Surgery is the only possible curative approach and so represents the traditional first-line therapy. However, as most patients with NETs are diagnosed once metastases have occurred, they require chronic postoperative medical management with the aim of relieving symptoms and suppressing tumor growth and spread. Somatostatin analogues, such as octreotide long-acting repeatable (LAR), or lanreotide Autogel, can improve tumor control, as demonstrated by recent placebo-controlled, double-blind, prospective randomized studies (Promid and Clarinet), although for limited lengths of time. Recent advances in our understanding of the molecular pathogenesis of these tumors are making targeted molecular therapy a possibility for the first time, improving the survival of patients with metastatic disease and an otherwise bleak prognosis. Biological treatments such as the mTOR inhibitor everolimus, or the tyrosine kinase inhibitor sunitinib, have mainly demonstrated tumor stabilization effect in pancreatic NETs. During the last year, new exciting data coming from recent phase III clinical trials have shown promising effects for everolimus in patients with lung and unknown origin NETs (Radiant-4 study), for peptide receptor radiotherapy (PRRT) with ^{177}Lutetium-DOTATATE in intestinal NETs (Netter-1 study), as well as for telotristat etiprate in patients with uncontrolled carcinoid syndrome (Telestar study). During the next few years, several randomized prospective clinical trials are expected to provide more insights regarding the role of new agents and their combinations, the timing and sequencing of different therapeutic options in the treatment approach for patients with advanced NET

The Role of a Second RAI Treatment in DTC Patients with Loco-Regional Neck Persistent/Recurrent Disease

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Introduction: Radioactive iodine (RAI) treatment is often indicated after total thyroidectomy in patients with differentiated thyroid cancer (DTC). However, the role of repeated RAI treatments for persistent/recurrent loco-regional DTC is unclear.

Objective: To investigate the impact of a second RAI treatment in patients with DTC who had an incomplete biochemical/structural response to initial treatment with no evidence of distant metastases.

Methods: Files of patients diagnosed with DTC in 1991-2013 who underwent at least two RAI treatments at a single institution were reviewed for clinical, biochemical, and imaging data. Exclusion criteria were receipt of <50 mCi at initial treatment and distant metastases. Thyroglobulin levels and neck ultrasound findings were compared before and 1-2 years after the second RAI treatment.

Results: The cohort included 189 patients (175 PTC type, 122 female, mean age 47.6+16.7 years). Of the 141 patients who did not undergo reoperation for loco-regional recurrence before the second RAI treatment, 57 had imaging findings compatible with nodal metastases. After the second treatment, lesion size decreased in 2, increased in 20, and remained stable in 27. No clear data was available for the remaining 8 patients. Mean stimulated thyroglobin level was 69.6±100.2 ng/ml before the second treatment and 81.8±106.1 ng/ml after (p=NS). In the other 84/141 patients, who had detectable thyroglobulin and no structural findings, stimulated thyroglobin level decreased from 33.6±49.8 to 16.8±47.2 ng/ml (p=0.001).

In the 48 patients who underwent neck reoperation prior to the second RAI treatment, there was no significant difference in stimulated thyroglobin level before and after the second treatment (p=0.15). Twenty still had suspicious sonographic findings 1-2 years later.

Conclusions: A second RAI treatment does not improve sonographic or biochemical findings in patients with DTC showing an incomplete structural response to initial treatment. In patients with only biochemical evidence of residual disease, the second treatment significantly decreases thyroglobulin levels.

Familial Central Hypothyroidism Caused bya Novel IGSF1 Gene Mutation

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Context: Congenital hypothyroidism of central origin (CH-C) is a rare disease in which thyroid hormone deficiency is caused by insufficient thyrotropin stimulation of an otherwise normal thyroid gland. A recently described syndrome of isolated CH-C and macroorchidism was attributed to loss-of-function mutations of the immunoglobulin superfamily, member 1 gene (*IGSF1*).

Patients and Methods: CH-C was diagnosed in three siblings. *TRH*, *TRHR* and *TSHB* were sequenced followed by whole-exome sequencing in the proband. A mutation identified in *IGSF1* was analyzed by direct PCR sequencing in family members. The effects of the mutation were assessed by *in-vitro* studies in HEK293 cells.

Results: The index case was negative for mutations in *TRH*, *TRHR* and *TSHB*. Whole-exome sequencing revealed a novel insertion mutation in *IGSF1*, c.2284_2285insA, p.R762QfsX7, which was confirmed by direct PCR sequencing and was identified in additional six family members. The mutation introduces a frame shift and premature stop codon in the 7th Ig loop, thereby truncating IGSF1. *In vitro* studies revealed that the mutated IGSF1–R762QfsX7 migrates as a doublet at ~28 kDa, which is far smaller than the wild-type protein (130-140 kDa). Both bands were EndoH-sensitive, indicating immature glycosylation and failure of the protein to traffic out of the endoplasmic reticulum to the plasma membrane. Further phenotypic findings in the family included macroorchidism and infertility in the uncle and mild neurological phenotype in the affected males like hypotonia, delayed psychomotor development, clumsy behavior and attention deficit disorder.

Conclusion: We identified a novel insertion mutation in *IGSF1* gene and further delineated the phenotype of IGSF1-deficiency syndrome. Our findings indicate an association between an *IGSF1* mutation and a neurological phenotype and of the possible effect of macroorchidism in this syndrome on male spermatogenesis.

High Dose Radioiodine Therapy Affects Ovarian Reserve in Women with Differentiated Thyroid Cancer

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Women undergoing radioiodine (RAI) therapy are advised to refrain from conceiving for 6-12 months following treatment as ovaries are exposed to radiation. However. it is still unclear if RAI treatment entails an irreversible damage to the ovaries. We sought to assess the effect of RAI on the ovarian reserve of premenopausal women undergoing treatment for differentiated thyroid cancer (DTC) by prospectively examining blood levels of anti-Müllerian hormone (AMH).

Subjects and Methods: Thirty women (aged 33.3±1.4), scheduled to undergo RAI treatment after surgery, were enrolled. Blood levels of AMH were assessed by immunoassay at baseline, and every 3 months for up to 1 year following RAI.

Results: To this date, 23 women, all AJCC Stage 1, were treated at a mean dose of 110.7±9.9 mCi (30-150). Of those, 19 have been reevaluated after treatment. Baseline AMH levels were 3.3 ±0.5 ng/ml. A 45% decrease in AMH levels was observed 3 months after treatment (1.8±0.4 ng/ml, $P<0.0001$). The level improved somewhat afterwards, but remained significantly lower than at baseline at 6, 9, and 12 months (2.4±0.5, 2.4±0.5, and 2.3±0.6, respectively). As most of these subjects had received high doses RAI of 100 and 150 mCi, we could not determine if there was a dose effect. In order to examine this issue, we grouped the 4 subjects who had received an ablative dose of 30 mCi for DTC with 5 women who had been treated with RAI for Graves` disease in doses ranging from 10-22 mCi. In these 9 subjects AMH levels did not change after treatment. They were 2.5±0.8, 2.4±0.8, 2.5±0.8, 2.5±1.0, and 2.2±0.8 ng/ml, at baseline, 3, 6, 9, and 12 months respectively.

Discussion and Conclusions: Large doses of RAI given as adjunct therapy to women with DTC appear to impair ovarian reserve as assessed by AMH levels. In contrast, lower doses up to 30 mCi, appear to be innocuous. This piece of data adds further weight to the precautions currently advocated with regards to RAI therapy in low risk DTC subjects.

A Novel Mutation (S54C) of the *PAX8* Gene in a Family with Congenital Hypothyroidism and High Proportion of Affected Individuals

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Introduction: Congenital hypothyroidism (CH) is a common congenital endocrine disorder with an incidence of 1:3000 to 4000 worldwide. Paired box transcription factor 8 (PAX8) is a thyroid transcription factor that plays an important role in thyroid organogenesis and development. To date more than 20 different PAX8 gene mutations causing thyroid dysgenesis have been reported. We report a novel mutation in PAX8 gene in a large family with variable phenotypic presentation.

Methods / Case Presentation: Four generations of a Hungarian Jewish family were affected. In the two generations studied all 4 siblings and 8 of 10 offsprings were affected. Five were diagnosed at birth (TSH 21-442 mU/L) and 7 were diagnosed at 2-30 years of age (TSH 6-18 mU/L). One affected individual had thyroid hemiagenesis on ultrasound and 6 had neurological and cognitive abnormalities, including, Parkinsonism, psychomotor developmental disorder and attention deficit disorder.

Results / Discussion: Direct sequencing of the PAX8 gene, revealed a novel single nucleotide substitution (c.162 A>T) resulting in the replacement of serine-54 with cysteine (S54C), which segregated with elevated serum TSH levels. These findings confirm the important role of PAX8 in the development of the thyroid gland. The mutation is located in a highly conserved area of the gene, which encodes the DNA-binding domain of PAX8. Other mutations of the same amino acid (S54G and S54R) have been also shown to exhibit functional impairment (decreased DNA binding and impart decreased transcriptional activity of the thyroperoxidase and thyroglobulin promoter).

Conclusions: We report a novel mutation of the PAX8 gene causing autosomal dominant CH with variable expressivity. The unusual features are high proportion of affected individuals (12 of 14) and neurocognitive abnormalities (6 of 14).

Disease Status at Presentation and Disease Related Mortality from Differentiated Thyroid Cancer

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Background: The current trend is non-aggressive treatment in low risk thyroid cancer patients. This approach is partially based on the fact that disease related mortality (DRM) from differentiated thyroid cancer is rare, affecting 1-2% of patients, typically with aggressive disease at presentation. However, this permissive approach is questioned due to several studies which reported up to 11.6% DRM in low risk patients with long term follow-up.

Goal: To characterize the initial presentation of patients who will eventually die from disease.

Methods: Patients with documented DRM were included. The Rabin thyroid cancer registry and the Davidoff Head & Neck cancer clinic databases were reviewed for eligible patients. Data collection included initial pathology, surgical report, radioiodine scans, imaging, thyroglobulin (Tg), and antibodies.

Results: Fifty three patients with DRM were included, representing database of over 2,000 DTC patients. The median age at diagnosis was 62 years (range 22-83, 83% older than 45), with median survival of 9 years (range 1-36). Histology was PTC in 66%, poorly differentiated in 21%, follicular carcinoma in 11%, and follicular adenoma in 2%.Patients were initially categorized as high risk for recurrence in 92% of cases (in 5 cases due to high Tg levels), intermediate risk in 6% (three older patients with N1b disease), benign in one case (2%), and none was low risk. Most patients had upfront advanced disease stage (stage IV-88%, III-2%, II-2%, I-8%). All patients with stage I disease were

Conclusion: None of the patients with DRM had low risk features at presentation, supporting the current paradigm of less aggressive approach in this group.

Falsely High Free Thyroid Hormone Measurements in Pediatric Patients with Metabolic Disease Treated with High Dose of Biotin

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Immunoassays are subjected to a number of interferences giving abnormal results which may lead to unnecessary investigations and treatment. We present clinical cases in which biotin treatment could be involved in abnormal results of thyroid function tests (TFTs) obtained by immunoassays based on biotinylated antibodies/analogs. Three infants were admitted to intensive care unit (ICU) during 2015, in Edmond and Lilly Safra Children's Hospital, because of respiratory distress and neurologic deterioration. Laboratory tests at admission revealed severe lactic acidosis. Thorough investigation led to the diagnosis of mitochondrial disease. During their hospitalization, near normal TSH and extremely highly elevated fT4 and fT3 were measured (Beckman-DxI analyzer). Those results were discrepant from their clinical presentations; as neither had goiter, signs of thyrotoxicosis or family history of thyroid disorders.

To assess the possibility of assay interference, TFTs in the same samples were evaluated by alternative methodologies (ADVIA-Centaur and Autodelfia analyzers), demonstrating normal fT3 and only moderately elevated fT4, as well as normal levels of tT3 and tT4.

Medications given to the patients and DxI TFTs assay principles were reviewed, pointing to potential interference, due to biotinylated antibodies/analoges used in fT3 and fT4 assays; thus, excess biotin in patients' serum competes with the biotinylated antibodies/ analoges for binding sites on streptavidin, resulting in falsely high levels of the hormones. Indeed, fT3 and fT4 levels measured in samples obtained twelve hours after biotin intake, were significantly lower, compared with levels obtained in close proximity to biotin intake.

High dose biotin (≥ 10mg/day) is used therapeutically in some metabolic disorders. Furthermore, many patients are *taking biotin as dietary supplement.* Therefore, physicians need to be aware that biotin could cause assay interference, especially when test results are discrepant from the clinical picture; Awareness will avoid misdiagnoses and unnecessary treatments.

*Moran Gal and Rina Hemi contributed equally to this work

The Prevalence of Abnormal Thyroid Function Test in Low Risk Pregnant Women in Israel

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Background: The prevalence of thyroid dysfunction in early pregnancy in Israel is not known.

Objectives: To assess the rate of abnormal thyroid-stimulating hormone (TSH) tests in low risk pregnant women attending a community clinic in Israel.

Methods: We conducted a retrospective analysis of the charts of low risk pregnant women (n = 303) who had undergone a TSH screening during the first trimester of pregnancy at Clalit Health Services Women`s Health Centers in Ashkelon and Tel Aviv. TSH of 0.1-2.5 mIU/L during the first trimester was considered to be normal.

Results: The TSH levels ranged from 0.04 to 13.3 mIU/L (median 1.73 mIU/L, mean 1.88 mIU/L).The rate of abnormal TSH was 25.6%, with low TSH 2.3% and high TSH 23.4%. The prevalence of abnormal TSH was not influenced by gravidity (primigravidas versus multigravidas) or place of residence (Ashkelon or Tel Aviv).

Conclusions: In view of the high prevalence of abnormal TSH (25.6%) in pregnant women in Israel during the first trimester, a universal country-wide screening should be considered.

The actual incidence of Small for Gestational Age (SGA) newborns and their catch-up growth is dramatically lower than previously considered.

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Background: SGA is defined as birth weight under 2 standard deviations (SD) from the mean. Previous studies indicate that 10% of SGA babies do not have "catch-up growth" (CUG). They are eligible for growth hormone (GH) therapy to increase final height. The unexpected low demand for GH therapy in SGA babies, triggered us to find the actual incidence of SGA and failure in CUG.

Methods: Our data included the registry of all-43,417 babies born at Hadassah hospitals between 2008-2011. SGA was defined according to the 2005 Dolberg`s (SGA2SD) table for Israeli newborns (similar to WHO parameters). Our calculated birth weight percentiles were compared to the nationally/internationally used percentile data (NUPD). Follow-up measurements of height and weight were obtained in mother and child centers or at the pediatrician.

Results: Only 573 babies in the cohort (1.32%) were SGA (57% of expected). This finding was consistent annually. Birth weight percentile comparisons showed that 1st and 5th percentile weights in our cohort were significantly (20%) higher while the 95th and 99th percentiles were 5% lower than the NUPD. Premature babies showed an even greater difference. CUG parameters (currently available for 295/573 SGA) indicated that 271 (91.9%) had CUG in the first 3 years (height 2.5SD below the mean). Of the other "short" 24 patients, 11(45%) had serious concomitant disease.

Discussion: This large cohort representing a heterogeneous (socioeconomic status and multiethnic) western Caucasian population indicates that the actual number of SGA newborns is nearly half of the expected according to WHO/NUPD definitions. The incidence of infantile CUG is also significantly higher than previously reported. These findings may have an impact on morbidity, health cost planning and GH requirements in SGA babies. Similar European and American studies are indicated to reassure both this decreased incidence and the decrease in the actual amplitude of the SD`s.

Growth without Growth Hormone: Can Growth and Differentiation Factor 5 be the Mediator?

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Growth without growth hormone (GH), is often observed in the setup of obesity; but the adipocytes- linear growth link is yet unknown. Conditioned medium (CM) of 3T3L1 cells induced to differentiate into adipocytes (adipocytes CM –CMA) was added to metatarsals bone culture and compared to CM from undifferentiated cells. CMA significantly increased metatarsals bone elongation. Adipogenic differentiation increased expression of growth and differentiation factor (GDF)-5, also found to be secreted into the CMA. GDF-5 significantly increased metatarsal length; anti GDF-5 antibody treatment of the CMA significantly reduced the stimulatory effect. The presence of GDF-5 receptor (bone morphogenetic protein receptor; BMPR1) in metatarsal bone was confirmed by immunohistochemistry. Animal studies in food restriction rodents allowed to re-fed showed an increase in GDF-5 serum levels concomitant with nutritional induced catch up growth. These results show that adipocytes may stimulate bone growth and suggest an additional explanation to the growth without GH phenomenon.

The Effect of GH Treatment on Klotho Blood Levels in Children with Growth Hormone Deficiency

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Objective: Klotho is an aging-mudulating protein expressed mainly in the kidneys, which can be cleaved and shed from the membrane to act as a hormone. Several lines of evidence suggest a tight interaction between klotho and the GH-IGF-I axis. In a previous study we demonstrated decreased klotho levels in pediatric patients with organic growth hormone deficiency (GHD). We aimed to investigate the effect of GH therapy on klotho levels in children and adolescents treated for GHD.

Patients and Methods: Twenty-nine children and adolescents (Males=15, aged 12.2±3.3 years), treated with GH for GHD (mean duration 2.5±2.8 years) were included in this study. Nineteen patients had samples obtained both before and during GH treatment; ten patients had samples obtained only under GH treatment. Data from 59 growth hormone sufficient (GHS) pediatric patients was used as a reference. Klotho serum levels were measured using an α-klotho ELISA kit. Klotho secretion from tissue culture cells was evaluated by Western blot of proteins precipitate.

Results: As expected, patients` height-SDS, weight-SDS and IGF-I-SDS increased significantly with GH treatment ($p=0.009$, $p=0.02$, and $p<0.001$, respectively). Klotho levels increased significantly ($p<0.001$) under GH treatment (from 1321.5±691.5pg/ml to 3380±2120.1pg/ml), and were significantly (<0.001) higher compared to GHS participants (1645±778pg/ml). Fold–increase in klotho was significantly correlated ($r=0.63$, $p=0.004$) with fold-increase in IGF-I. No correlation was found between klotho levels under treatment and age, height-SDS, weight-SDS, BMI-SDS, GH dose, duration of treatment with GH, growth velocity or IGF-I-SDS. There was no difference in klotho levels between males and females and between pre-pubertal and pubertal participants. Finally, we showed that treatment of klotho-transfected HEK293 kidney cells with IGF-1 induces secretion of klotho to media.

Conclusions: We have shown, for the first time, an increase in klotho levels under GH treatment of pediatric patients with GHD. This increase was associated with an increase in IGF-I levels. We suggest a mechanistic explanation as IGF-1 induced secretion of klotho from cells. Our findings add further support for the close association between klotho and the GH/IGF-I axis, and may help to discern the nature of this interaction. Under GH treatment, klotho levels reached supra-physiological levels. The clinical significance of this finding is still to be elucidated.

2nd Year Efficacy Results of Once-Weekly Administration of CTP-Modified Human Growth Hormone (MOD-4023): A Phase 2 Study in Children with Growth Hormone Deficiency

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Objective: Growth hormone (GH) replacement therapy currently requires daily injections. This may cause poor compliance, inconvenience and distress for patients. CTP-modified hGH (MOD-4023) has been developed for once-weekly administration in growth hormone deficient (GHD) adults and children. The 18 and 24 month efficacy of once-weekly subcutaneous (SC) administration of MOD-4023 was evaluated in a Phase 2 study in children with GHD.

Design and Methods: A one year, randomized, controlled Phase 2 study was conducted in 53 pre-pubertal children with GHD, who received once-weekly SC injections of one of three MOD-4023 doses (0.25, 0.48, and 0.66 mg/kg/week) vs. daily hGH (34 µg/kg/day). Forty-six subjects were rolled over to continue with the same MOD-4023 dose in an open-label extension (OLE), which will routinely assess growth until marketing approval. Height velocity (HV) results during the 2nd year of MOD-4023 treatment for 45 patients were compared to historical controls[1]. Serum concentrations of IGF-1 and IGFBP-3 were monitored, as well.

Results: The analysis included 2nd year height velocity data for 45 patients. All 3 doses of MOD-4023 demonstrated promising 2nd year growth, while the two higher doses of MOD-4023 resulted in better growth in comparison to the lower dose of MOD-4023 (0.25 mg/kg/week), and in line with reported age- and GHD severity-matched historical controls[1].

Conclusions: The efficacy of single weekly administration of MOD-4023 for the treatment of pediatric GHD patients was further confirmed during the 2nd year of treatment as part of the OLE of a Phase 2 study. This further affirms that a single weekly injection of MOD-4023 has the potential to replace daily hGH injections in children with GHD and provides additional efficacy data to support dose selection for OPKO's upcoming Phase 3 trial.

References

[1] Ranke et al., 2010

Disclosure: RGR: consultant for OPKO Biologics. KR, OM: Investigator, Ascendis Pharma. Nothing to disclose: NZ, JS, ZZ, RK, LA, OH, GH.

Outcome of Adolescents Undergoing Sleeve Gastrectomy–One Year Follow-Up

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Bariatric surgery in adolescents is gaining popularity, also in Israel. The main surgical technique that is done on adolescents in Israel is a laparoscopic sleeve gastrectomy.

The aim of the study was to describe the clinical and laboratory outcomes of adolescent patients one year after they underwent sleeve gastrectomy.

Anthropometric clinical and laboratory data were obtained from all patients age 13-19 years old that had bariatric surgery between Jan 2010 and March 2015 in Edmond and Lily SafraChildren's hospital, Sheba Medical Center, Israel.

Results:

The study population comprised of 32 adolescents (M=18/F=14).

Their mean±SD age at surgery was 16.5±1.36 years (range 13.7-18.6).

Mean follow up after the surgery was 13.7±7.6 (range 3-36) months.

After one year follow-up BMI decreased from 46.85 kg/m2to 32.4 kg/m2 BMI z score was reduced from 2.78 to 1.87. ($p<0.001$).

Weight loss was more significant in males ($p=0.0009$) and with older age, above 17 year ($p=0.0415$)

Patients with HOMA-IR >4 before the surgery reduced less weight ($p=0.0049$).

During follow-up most obesity related comorbidities have resolved. Dyslipidemia resolved in 73% of the patients ($p <0.0001$), HTN resolved in 80% ($P=0.0005$) and metabolic syndrome present in 65% of the patients before surgery resolved completely.

Nevertheless there were severe complications that developed after the surgery including readmission (20%), symptomatic cholelithiasis requiring laparoscopic cholecystectomy (16%), nonspecific eating disorders in 2 patients, one patient developed paralysis secondary to severe vitamin B1 deficiency. Three of our patients were re-scheduled for re-operation (one had roux and Y bypass and two had re-sleeve gastrostomy).

Conclusions:

Sleeve gastrectomy in adolescents improves BMI and comorbidities significantly after one year follow-up.

Weight loss reduction is greater in males and older adolescents and less in patients with insulin resistance.

Despite significant weight loss and comorbidities improvements, bariatric surgery in adolescents is associated with significant long-term morbidity

A GLP-1 Receptor Agonist Improves Beta-cell Function in Type 2 Wolfram Syndrome While Preventing Mitochondrial Iron Overload

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Background: Wolfram syndrome is a multisystem neuronal and beta-cell degenerative, progressive and irreversible disorder. Type 2 Wolfram syndrome (T2-WFS) results from a missense mutation in the *CISD2* gene, encoding an ER and mitochondrial outer and their interacting membranes, 2Fe-2S protein, called NAF-1. We treated a patient with T2-WFS with the GLP-1 receptor agonist (GLP-1-RA) Exenatide for 9 weeks; this enabled to reduce the daily insulin dose by ~70%, while maintaining adequate glycemic control. Pre-meal injection of Exenatide prevented post-prandial hyperglycemia, despite severe insulin deficiency prior to treatment. Further, an IV glucose/glucagon/arginine stimulation test, performed off-drug, showed 7-fold increase in maximal insulin secretion.

Objective: Clarifying the mechanisms underlying beta-cell dysfunction in T2-WFS and the beneficial effects of GLP-1-RA.

Methods: We generated a beta-cell T2-WFS model by knocking down NAF-1 in rat insulinoma beta-cells. Glucose-stimulated insulin secretion (GSIS) in the NAF-1 knockdown cells was determined by a rat insulin ELISA kit. Mitochondrial membrane depolarization, labile iron and accumulation of reactive oxygen species (ROS) in the knockdown cells were measured by fluorescence probes and analyzed microscopically. The expression of the oxidative stress maker, TXNIP was analyzed by Western blotting.

Results: NAF-1 repression (~50%) decreased GSIS by ~50%, while the response to cAMP was preserved. Greater insulin secretion of NAF-1 knockdown cells was observed in response to Exenatide, forskolin and IBMX. NAF-1 knockdown increased mitochondrial labile iron accumulation, along with mitochondrial membrane depolarization, accumulation of ROS and increased TXNIP protein level. Treatment with Exenatide and the iron chelator DFP prevented mitochondrial dysfunction. Exenatide also decreased TXNIP expression.

Conclusion: NAF-1 deficiency has opposing effects on insulin secretion: GSIS is impaired probably due to mitochondrial dysfunction and oxidative stress, whereas the response to cAMP is enhanced through yet unknown mechanism. NAF-1 deficiency impairs iron homeostasis, resulting in mitochondrial dysfunction and oxidative stress that could be prevented by iron chelation and GLP-1-RA. Treatment with GLP-1-RA should be considered in WFS and probably other iron overload disorders.

Autoimmune Diseases and Manifestations of Metabolic Syndrome in Turner Syndrome – Comparison Between 45,X0 and Other X Chromosome Abnormalities

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Context: Turner syndrome (TS) is a genetic disorder caused by X chromosome monosomy (45,X0) or partial absence of the second sex chromosome, with or without mosaicism. An increased frequency of autoimmune diseases and metabolic disorders has been observed in Turner patients.

Aims: To compare Turner monosomy (karyotype 45,X0) to the other X chromosome abnormalities with regards to occurrence of autoimmune diseases and metabolic disorders.

Design: Retrospective study of 103 TS patients followed during 1960-2013.

Setting: Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel.

Results: Monosomy 45,X0 was found in 31/103 (30%) of the cohort. The average age of diagnosis was younger in 45,X0 compared to the other X chromosome abnormalities (6.2 ± 5.5 vs. 9.4 ± 4.8 years, $P = 0.004$). Duration of follow-up (14.0 ± 8.8 years), and age at patient`s last visit (21.9 ± 9.6 years) were similar. Prevalence of autoimmune diseases [autoimmune thyroiditis (45.6%) and positive celiac serology (7.1%)], the number of diseases and age at onset were similar in both groups. BMI (adjusted for TS) increased during follow-up; obesity at last visit was more prominent in girls with 45,X0 ($P = 0.013$). The percentage of patients with impaired glucose metabolism increased during follow-up: impaired fasting glucose (> 100mg/dL) from 10.6% to 17.9%; impaired glucose tolerance (140-199 mg/dl) from 23.8% to 30.5% and elevated HbA1c (> 5.8%) from 12% to 16.7%. At last clinic visit, lipid profile levels were above the 90th percentile for total cholesterol, LDL-cholesterol and triglycerides in 29.1%, 23.5%, and 30.1% of the patients, respectively; systolic blood pressure was increased in 52.3% and diastolic blood pressure in 18.2% of the cohort. The prevalence of disturbances in glucose metabolism, lipid profile, and blood pressure were similar in both groups.

Conclusions: In Turner syndrome, an increased risk of autoimmune diseases and metabolic disorders were found regardless of the karyotype. Careful surveillance and early intervention in patients with 45,X0 and increased weight gain is warranted in an attempt to prevent obesity and thereby their risk for development of metabolic disorders.

Pigment Epithelium Derived Factor Targets Both Angiogenic and Cytokine Pathways in the Pathogenesis of Ovarian Hyperstimulation Syndrome

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Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of ART induced by an ovarian release of vasoactive, angiogenic substances resulting in vascular leakage. The consequent ascites is attributed to hCG-induced VEGF, as well as to lysophosphatidic acid (LPA)-induced angiogenic cytokines interleukin (IL)-6 and IL-8.

We aimed to examine the putative role of the anti-angiogenic and anti-inflammatory mediator, pigment epithelium derived factor (PEDF), as a physiological negative regulator of both VEGF and the angiogenic cytokines networks.

We used a mouse OHSS model and cultured granulosa cells (primary-human; cell line- rat). Changes in PEDF and VEGF were measured by PCR and western blot. OHSS symptoms were recorded by changes in body and ovarian weight and in peritoneal vascular leakage (Miles permeability assay).

We found that OHSS was correlated with hCG-induced impaired PEDF/VEGF ratio, and LPA-induced impaired PDEF/IL-6/8 ratio. Interestingly, GnRH agonist (GnRH-a) triggering, that is known to prevents OHSS, modulated PEDF/VEGF ratio inversely to hCG triggering both in vitro and in vivo. Treatment with recombinant PEDF (rPEDF) reduced hCG-induced VEGF and LPA-induced IL-6/8 levels in vitro. Moreover, in vivo rPEDF treatment alleviated OHSS signs and reduced ovarian VEGF and IL-6 levels.

These observations provide a new perspective into the paramount role of PEDF in the pathophysiology of OHSS, namely, the low expression level of PEDF which enables high expression levels of both VEGF and IL6. Exploring the combined anti-angiogenic and anti-inflammatory properties of PEDF in the female reproductive system could open new therapeutic avenues for other fertility and gynecological pathologies.

Severe 5 Alpha Reductase 2 Deficiency with Aphallia is Caused by Y91H Mutation in SRD5A2 Gene - Challenges in Diagnosis and Treatment

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Background: 5-alpha-reductase-2 (5a-RD2) deficiency is an autosomal recessive 46,XY disorder of sexual development (DSD), characterized by undervirilized prepubertal males with inguinal testes, and ambiguous genitalia. At Puberty, the rise in testosterone and elevated 5α-RD1 isoenzyme activity result in virilization, and often in gender identity change. Precise diagnosis in DSD is critical for treatment, gender assignment and for anticipating adult function.

Objective: To elucidate the genetic cause, the pathophysiology and the optimal treatment for a unique 46,XY DSD patient.

Methods and Results: Consanguineous Palestinian parents requested a change to male gender assignment in their 2.5 years old girl. The girl had labial embedded testis, aphallia, high anogenital ratio (o.78) indicating testosterone responsive genitalia (>0.5), XY karyotype, normal basal and ACTH stimulated glucocorticoids levels, high HCG stimulated testosterone and a testosterone/androstenedione ratio of 2.4. Given the high testosterone and the high anogenital ratio, we sequenced the SRD5A2 gene and found a new 271 T to C, Y91H mutation, in an exon encoding 5α-RD2 transmembranal domain. Urinary steroid metabolites profile showed a dramatically decreased ratio between 5alpha/5beta metabolites of corticosteroids indicating a decreased function of the mutated 5α-RD2 in this case.

The rare phenotype of absence of clitoromegaly and complete aphallia with seemingly impossible surgical penile reconstruction, complicated the adherence to the parents` request for male gender assignment. A trial of local dihydrotestosterone administration resulted in dramatic enlargement of the rudimentary clitoris.

Conclusion: The new Y91H mutation in the SRD5A2 gene, causing a severe reduction in the alpha reductase activity as reflected in urine metabolites, results in a rare XY-DSD phenotype with complete aphalia.

The prepubertal use of local dihydrotestosterone may alleviate the conflict between male gender assignment and a complete female phenotype.

Further studies correlating SRD5A2 enzymatic activity to genotype and phenotype may contribute to early comprehensive decisions regarding gender assignment.

Construction of a Three Dimensional In Vitro Embryo Implantation Research Model Using Alginate Macro-porous Scaffold

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Implantation failure remains an unsolved obstacle in reproductive medicine and is a major cause of infertility in otherwise healthy women. Indeed, only about 20% of embryos transferred to the uterus, following in vitro fertilization (IVF), lead to the birth of a healthy infant. Due to obvious ethical restrictions there is an unmet need to establish an in vitro model that mimics the events in the uterine wall during the implantation process. The available two-dimensional models do not represent fully the event taking place at implantation.

Alginate scaffolds were prepared by a freeze-dry technique. Uterine epithelial RL95-2 and non-receptive HEC-1A cell lines were seeded into scaffolds, cultivated in four different media: 3 weeks in Estrogen containing, Progesterone containing or without hormone addition media, or one week priming of Estrogen, following by two weeks of Progesterone containing medium. E-cadherin mRNA expression levels, evaluated by qPCR, were shown to be hormone-dependent and time-dependent in RL95-2 cell constructs, in contrast to HEC-1A cells, where no hormonal effect was evident. In 2-week old RL95-2 constructs, Estrogen treatment significantly increased E-cadherin mRNA expression, compared to other hormone treatments.

E-cadherin immuno-staining of cell constructs revealed pronounced protein expression on cell membranes of RL cell constructs, compared to HEC-1A. In order to evaluate cell constructs receptivity to trophoblast, JAR spheroids were seeded on top of 3 week-old cell constructs and incubated for 24 h. Attachment of JAR spheroids to RL95-2 culture was evaluated by H&E staining. JAR attachment was not evident in HEC-1A constructs.

Our 3D culture models within macro-porous alginate scaffolds enabled long-term culture of viable cells, and may serve as a research model for regulatory mechanism governing implantation process and evaluation of potential novel therapeutic strategy for regulating implantation defects and restoring the ability to implant embryos in patients with repeated implantation failure (RIF).

A Variant in a Mitochondrial-tRNA Processing Regulator Gene Causes Ovarian Dysgenesis and Sensorineural Deafness (Perrault Syndrome)

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Perrault syndrome is a rare autosomal recessive disorder characterized by sensorineural hearing loss (SNHL) in both sexes and primary ovarian insufficiency in 46, XX karyotype females. To date, biallelic variants in five causative genes, *HSD17B4*, *HARS2*, *LARS2*, *CLPP* and *C10orf2*, have been reported to cause this rare phenotype. Four of these genes encode proteins important in the synthesis or degradation of mitochondrial proteins.

We report a consanguineous Palestinian family with three sisters affected by profound bilateral SNHL and primary amenorrhea due to absent ovaries. Autozygosity mapping by Affymetrix v6 SNP array of the sibship, including two unaffected brothers and two unaffected sisters revealed three homozygous regions >2Mb shared between the affected individuals. An exome of one affected individual identified a single homozygous novel missense variant c.1454C>T; p.(Ala485Val) in the autozygous regions that was absent in 100 ethnically matched controls, 700 in-house exomes and public databases of over 66,500 exomes and segregated with the phenotype. The variant was predicted to be deleterious by *in silico* tools and the residue is conserved to a plant ortholog.

The identified gene encodes a protein responsible for the processing of mitochondrial (mt) pre-tRNA. Functional assays showed that the variant caused an *in vitro* reduction in pre-tRNA processing of approximately 35-40% and that there is an accumulation of unprocessed mt pre-tRNA transcripts in fibroblasts from an affected individual. Compared to wild-type, the variant protein exhibits a similar level of structural integrity, but altered patterns of complex formation. Our findings expand the number of genes that cause Perrault syndrome and reinforces the importance of mitochondrial homeostasis to ovarian function.

Menopause Is a Low Sirtuin1 State: The Ovariectomized Mouse Model

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Menopause is a period of accelerated aging in women. It is associated with weight gain, blood pressure elevation and an increased risk of developing dementia. Sirtuin1 is a cellular energy sensor and a major player in metabolism and aging. Sirtuin1 over-expression confers protection against diabetes, obesity and dementia in mice. We asked if Sirtuin1 plays a role in the metabolic changes that occur with the menopausal transition.

To test the hypothesis that Sirtuin1 level or activity is altered with OVX, 9-week-old female mice were subjected to OVX or SHAM operation, and were left untreated for 6 weeks. OVX and SHAM mice were sacrificed 1 and 6 weeks post operation. The remaining OVX mice were treated for 6 weeks with either 17-β estradiol, SRT3025, a Sirt1 activator or a vehicle. SHAM mice were left untreated. Upon sacrifice uterine weight was determined to ensure a successful OVX. *In vitro* experiments were conducted in a model cell line.

OVX induced a significant weight gain of 27% and a 61% decrease in uterine weight over the 12 week period. Treatment with SRT3025 significantly blunted OVX-induced weight gain better than estradiol treatment. Uterine weight was similar in OVX untreated and OVX SRT3025-treated mice, suggesting no uterine estrogen-like effect. Strikingly, a 40% decrease in Sirtuin1 protein level was observed 6 weeks post operation in liver and brain obtained from OVX compared to SHAM mice. Liver Sirtuin1 mRNA expression was significantly elevated in OVX compared to SHAM mice. To elucidate underlying mechanisms, C3H10T1/2 cells were exposed to estradiol, fulvestrant or serum derived from OVX and SHAM mice 1 week post operation. While no effect in Sirtuin1 protein level was detected in estradiol and fulvestrant-treated cells, serum derived from OVX mice induced a decrease in Sirtuin1 expression, suggesting that OVX-related humoral factors influence Sirtuin1 expression.

In conclusion, reduced Sirtuin1, that appears to result from indirect effects of estrogen withdrawal, is a possible contributor to OVX-induced weight gain. Pharmacologic activation of Sirtuin1 blunted OVX-associated weight gain without inducing an undesired increase of uterine weight. Future studies are needed to evaluate the effects of Sirt1 activation on menopause-related metabolic derangements.

The Role of Angiogenesis in the Selection of Dominant Follicles

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It is commonly accepted that the establishment of dominance among the ovarian follicles is enabled by the formation of a rich vascular network, which allows the increased delivery of gonadotropins. We propose that in addition to their ability to establish unique vascular features, the dominant follicles (DF) secrete anti-angiogenic factors, thus inhibiting angiogenesis and further development of the neighboring, subordinate follicles (SF). The aims of our study are to characterize early vascular modifications distinguishing the DF, and to explore the involvement of anti-angiogenic factors in the process of DF selection. Dynamic contrast enhanced (DCE) MRI studies showed that upon selection of the DF, total ovarian blood volume is elevated, and more areas with high blood volume are detectable. In addition, the ovary demonstrates a local increase of permeability after DF selection in close topographic correlation with large antral follicles. We also show that soluble vascular endothelial growth factor receptor (sVEGFR1/sFlt), a potent anti-angiogenic factor, is upregulated in concomitance with DF selection. Moreover, large follicles isolated from ovaries of mice treated with the FSH analog, PMSG, secrete higher levels of sFlt than small follicles. Our results demonstrate unique vascular characteristics of the DF in the mouse ovary, potentially establishing a novel tool for their detection. Furthermore, our findings support a possible link between anti angiogenic factors and the cross talk between DF and SF.

The Role and Regulation of the DNA-modifying Tet Enzymes in the Pituitary Gonadotropes

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Tet enzymes catalyze DNA hydroxymethylation and sometimes demethylation, and thus have a central role in the regulation of gene expression. We have shown that Tet1 and Tet2 are expressed in the pituitary gonadotropes, and have distinct effects on the expression of the *Lhb* gene, with Tet1 repressing its expression in immature partially-differentiated gonadotropes, and Tet2 having a stimulatory effect. Tet1 is dramatically down-regulated with differentiation of the gonadotropes and is not expressed together with *Lhb* in mature fully-differentiated gonadotropes. This led us to study how the Tet enzymes are regulated in these cells, and we found that GnRH has a strong inhibitory effect on Tet1 while activating Tet2, both of which appear to be via activation of protein kinase A. Tet1 is also repressed via protein kinase C and calcium-activated pathways. In addition, we found that estradiol inhibits Tet1 expression, and that the estrogen receptor, ESR1, binds upstream of Tet1 gene promoter suggesting that the effect is mediated directly. To confirm the effect of the gonadal steroids *in vivo*, we performed ovariectomy and castration in mice and measured Tet1 levels and gonadotropin gene expression in the gonadotropes after various time frames. In both cases, gonadectomy led to a clear increase in gonadotrope cell numbers and the cell proliferation was accompanied initially by an increase in Tet1 mRNA levels with low levels of *Lhb*, but Tet1 levels then dropped, accompanied by an increase in those of *Lhb*. These results confirm the physiological regulation of Tet1 by the gonadal steroids and the requirement of its down-regulation for completion of gonadotrope differentiation. Our results thus reveal novel epigenetic pathways though which mammalian reproductive function is controlled and also shed further light on the role and regulation of Tet enzymes in gene expression in differentiated cells.

Poster presentation

Group 1: Diabetes

Peripherally-Restricted Cannabinoid-1 (CB_1) Receptor Blocked Attenuates Type-1 Diabetic Nephropathy in Mice

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Diabetic nephropathy (DN), a worldwide progressive kidney disease that affects approximately 30% of patients with diabetes, is strongly associated with cardiovascular morbidity and mortality. Altered activation of the endocannabinoid/cannabinoid-1 (CB_1) receptor system has been recently demonstrated in various diabetic complications, including DN. CB_1 receptors are expressed in various renal cells and play an important role in the onset of nephropathy. Their blockade with globally-acting CB_1 receptor antagonists improves renal function, reduces albuminuria and glomerular lesions in murine models of DN. However, their therapeutic value is limited by neuropsychiatric adverse effects mediated at CB_1 receptor in the CNS, such as depression, anxiety and suicidal ideation.

Here we describe the renal effect of the novel peripherally-restricted CB_1 receptor antagonist, JD5037, in mice with streptozotocin (STZ)-induced Type-1 DN. Blockade of the CB_1 receptor did not affect body weight, blood glucose, serum insulin and pancreatic damage. Yet, chronic 15-week oral treatment with JD5037 (3 mg/kg) ameliorated the STZ-mediated kidney structural and functional changes. Similarly with the brain-penetrant CB_1 receptor antagonist, SLV319, administration of JD5037 to diabetic mice caused a significant reduction in glomerular filtration rate, albuminuria, and serum urea, and normalized the expression and urine levels of several kidney injury markers. Furthermore, peripherally-restricted CB_1 receptor blockade completely attenuated kidney fibrosis and inflammation.

In conclusion, in a rodent model of DN, targeted blockade of CB_1 receptor in periphery has the potential to treat renal abnormalities associated with Type-1 diabetes. Therefore, our findings could further support the clinical development and testing of peripherally-restricted CB_1 receptor antagonists for the treatment of DN.

Pediatric Type 1 Diabetes Mellitus Incidence and Anthropogenic Metals in the Environment - Results from Northern Israel

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Background/Aim: The unprecedented rise in type 1 Diabetes Mellitus (T1DM) incidence in children during the last decades calls for a study of potential environmental causes.

Methods: Pediatric T1DM incidence rate was calculated for the period 2002-2012 for 5 municipal sub-districts in northern Israel. The calculated rate is based on data obtained from the national T1DM registry and the Israeli central bureau of statistics. The rate was correlated (using multiple regression analysis and factor analysis) with data from the national geochemical mapping project which served as a means of distinguishing between anthropogenic contribution to natural background.

Results: The results show positive correlation between pediatric T1DM incidence and the presence of a suite of anthropogenic metals in the environment such as Antimony (Sb),Arsenic (As), Molybdenum (Mo), Zinc (Zn) Lead (Pb) and Chromium (Cr).

Conclusions: The results imply that anthropogenic changes in the environment contribute to the rising incidence of pediatric T1DM. Possible mechanisms will be discussed but require further research.

SHBG – A Mere *Bystander?*

SHBG - Overexpression Does Not Reduce Insulin Resistance, Obesity or Diabetes High Fat Fed Mice

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Background: Sex hormone binding globulin (SHBG) is a homodimeric plasma glycoprotein produced by the liver. It acts as the main transporter of biologically active estrogens and androgens in all vertebrae.

Low levels of SHBG have been linked to increased propensity for diabetes and metabolic syndrome. Specific genetic polymorphisms of SHBG gene that were predictive of levels of the SHBG protein, strongly predicted increased risk of type 2 diabetes in both men and women[1] [2]. Finally, an association between polymorphism in the SHBG promoter and polycystic ovary syndrome has been suggested[3]. Thus, it seems that the SHBG protein may have an active role in the pathogenesis of diabetes, rather than serving as a mere biomarker[4].

Aims: Analyze whether mice over-expressing human SHBG have lesser tendency to develop diabetes and other characteristics of the metabolic syndrome.

Methods: Transgene mice expressing human SHBG gene and their littermate control wild types mice were fed high fat diet (HFD).

Results: There was no difference in weight of transgene as compared to wild type littermates. Male transgenes had significantly higher muscle mass after 2-3.5 month HFD. Fasting blood glucose, as well as insulin or HOMA-IR or HOMA-IR divided by weight were not different in transgenic vs. wild type males. Female transgenes had significantly higher fasting glucose, with no difference in average insulin or HOMA-IR and HOMA-IR divided by weight. Glucose tolerance test (GTT) was no different. Overnight GTT was significantly lower in transgenic males. There was no difference in liver enzymes and triglyceride levels and blood pressure values.

Conclusion: In this model of transgenic mice overexpressing human SHBG, this protein showed no protection against diabetes and metabolic syndrome.

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New Onset Diabetes after Kidney Transplantation is Associated with Increased Mortality - a Retrospective Cohort Study

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Objective: Clinical outcomes in individuals with new onset diabetes after transplantation (NODAT) and the optimal treatment for this complication are poorly characterized. This study was intended to better define these issues.

Methods: Patients who underwent kidney transplantation and did not have diabetes prior to transplantation were included in this study and the clinical outcomes were compared between those who developed NODAT and those who did not. In those who developed NODAT, oral therapy was compared with insulin based therapy.

Results: A total of 266 kidney transplant recipients were included, of which 71 (27%) developed NODAT during the time of the follow up. Using Cox multivariate analysis adjusted for age and gender, hazard ratio for overall mortality among patients with NODAT versus those without NODAT was 2.69 (95% CI 1.04-7.01). Among patients who developed NODAT, 29 patients (40%) were treated with an insulin-based regimen. At the end of follow-up there no difference was found in mean HbA1c, and therapy regimen did not influence mortality.

Conclusions: NODAT in kidney transplants is associated with increased mortality compared with individuals without NODAT. Treatment with oral agents and insulin-based therapy seems to be equally effective in these patients.

The Prognostic Significance of Admission Blood Glucose Levels in Elderly Patients with Pneumonia (GAP Study)

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Aims: To evaluate the association between admission blood glucose (ABG) and short and long-term mortality following hospitalization for pneumonia of elderly patients with and without pre-existing diabetes mellitus (DM).

Methods: Historical prospectively collected observational data derived from the electronic records of hospitalized patient ≥65 years, admitted for pneumonia to medical wards, between January 2011 and December 2013. Data were analyzed for comorbidities and mortality. ABG levels were classified to five categories: ≤70 (low), 70-110 (normal), 111-140 (mildly elevated), 141-199 mg/dl (moderately elevated) and ≥200 mg/dl (markedly elevated). Main outcomes were all-cause mortality at various time points after adjustment for age, gender, hypertension, ischemic heart disease, congestive heart failure, cerebrovascular disease and corticosteroid treatment.

Results: The cohort included 2,164 patients, 743 with DM (mean age 81, 53% male) and 1,421 without it (mean age 83, 52% male). Most patients without DM (37%) had mildly elevated ABG, and most patients with DM (41%) had markedly elevated ABG. There was a significant interaction between DM, ABG and in-hospital, 30-days, and 12, 24 and 36 months mortality ($p \leq 0.05$). In patients without DM there was a significant association between ABG and all-cause mortality in the short and long-term ($p<0.0001$), while in diabetic patients there was no association between ABG and short- or long-term mortality. In patients without DM, compared with normal ABG, in-hospital mortality rates (adjusted hazard ratio, 95% CI) were higher with moderately and markedly elevated ABG (aHR = 1.5 and 2.7, respectively, $p<0.05$). 30-days mortality rates were higher with moderately and markedly elevated ABG (aHR = 1.4 and 1.9, respectively, $p<0.01$). Long-term results were similar at 12, and 36-months (aHR=1.3 and 1.8, respectively, $p<0.05$, for moderately and markedly elevated ABG).

Conclusion: In elderly patients hospitalized for pneumonia, moderately and markedly elevated ABG levels in those without DM is associated with increased short- and long-term mortality rates. In patients with DM there is no association between ABG levels and mortality.

Effect of Short- and Long-Term Diabetes Control on In-Hospital and One Year Mortality Rates in Hospitalized Patients with Diabetic Foot: What is the Most Effective?

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Introduction: Whereas optimized metabolic control undoubtedly plays a major role in preventing progression of microvascular as well as macrovascular diabetic complications, it is unclear whether patients with diabetic foot benefit from strict glycemic control. The present study was designed to investigate the effect of short- and long-term diabetes control on hospital outcomes including: in-hospital and one year mortality rates, length of hospital stay and rate of repeated admission in hospitalized patients with diabetic foot.

Methods: The study group consisted of 341 type 2 diabetic patients hospitalized from January 2008 through December 2012 in Wolfson Medical Center due to the diagnosis of diabetic foot. All glucose measurement performed during hospitalization are stored in the patients` health records. Adequate short –term glycemic control was defined as average glucose levels during admission in the range 110-180 mg/dL. HbA1c values below 7% was defined as adequate long–term glycemic control.

Results: The average glucose levels during hospitalizationwere 179±45 mg/dL and 39.6%±21.2% of the measurements were between 110-180 mg/dL. Mean admission HBA1c levels were 8.43%±2.26%, and 31% of the values were below 7%. The mean length of hospital stay was 24.3±22.6 days, 15.0% of the patients needed surgical intervention during admission, the in-hospital mortality rate was 10.3%, and the rate of 1-year readmission was 25.1%. In regression models, adequate diabetes control during hospitalization was marginally associated with reduced in-hospital mortality (OR 0.454, 95% confidence interval 0.186-1.103, p=0.081) and significantly with one year mortality (OR 0.269, 95% confidence interval 0.707-0.101, p=0.009). However, adequate diabetes control during hospitalization did not effect the length of hospital stay or rate of repeated admission.. HbA1c levels were not associated with any of the prognostic factors.

Conclusions: Improved glucose control during admission (levels between 110-180 mg/dL) is associated with reduction of one year mortality. HBa1C levels had no impact on these parameters in hospitalized patients with diabetic foot.

The Effect of Phlebotomy-Induced Hemolysis on Insulin Level Determination

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Objective: To examine the effect of phlebotomy-induced hemolysis on serum insulin and C-peptide measurement by an immunochemiluminometric (ICMA) assay.

Methods: As part of a study designed to evaluate β-cell function in a group of adults with newly-diagnosed type 2 diabetes, we tested insulin and C-peptide levels in 1,048 samples. In order to evaluate the effect of phlebotomy-induced hemolysis we determined insulin and C-peptide levels simultaneously in hemolyzed and non-hemolyzed samples.

Results: Forty- seven (4.5%) of the 1048 samples were affected by hemolysis. In 26 cases we had a paired hemolyzed and non-hemolyzed serum samples that allowed a simultaneous comparison. We found that all degrees of hemolysis led to a significant decrease of insulin level. In hemolyzed serum the median (IQ range) of the insulin was 5.6 (1.8-24.3) mIU/l vs. 21.3 (11.4-48.5) mIU/l in non-hemolyzed serum, representing 25%-98% loss. This phenomenon was not found for C-peptide levels.

Conclusion: Clinicians have to be aware that even mild degree of phlebotomy- induced hemolysis has a significant effect on serum insulin levels determination that can lead to misinterpretation of test results. This finding has important implication especially in the evaluation of suspected cases of hyperinsuIinemic hypoglycemia.

Comparison of Insulin Detemir and Glyburide treatment for Gestational Diabetes Mellitus

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Objectives: To evaluate the safety, efficacy and pregnancy outcomes of insulin detemir vs. glyburide treatment in women with gestational diabetes mellitus (GDM).

Methods: A retrospective cohort study of women with GDM who were treated with either glyburide or insulin detemir for GDM in a university-affiliated tertiary hospital. Treatment modality was determined according to physician preferences. Composite adverse neonatal outcome was defined as any: birthweight >90th percentile or ≥4000g, shoulder dystocia, clavicular fracture, hypoglycemia, jaundice or stillbirth.

Results: A total of 91 patients with GDM were enrolled. Glyburide and insulin detemir treatments were administered in 62 and 29 patients, respectively. Maternal age, pre-gestational BMI (29.0±5.9 vs. 31.5±8.4 kg/m^2, respectively, p=0.23) and rate of abnormal OGTT glucose values were not significantly different between groups.

Good glycemic control rates were comparable in both groups. However, hypoglycemic episodes were reported only in the glyburide group. (19.4% vs. 0%, p=0.01). Only one event of severe hypoglycemia was recorded in the glyburide group. In matched t-test, there was a significant increase in maternal weight gain during pregnancy among women in glyburide group (8.8±5.1 p<0.001) in comparison to those in IDet group (2.1±19.9 p=0.71). No difference in the rate of cesarean section was detected between the groups. One stillbirth was reported in the glyburide group. The rate of composite adverse neonatal outcome was significantly lower in the detemir vs. glyburide group (26.9 vs. 43.5%, p=0.04). However, in a multivariate analysis, this difference was not significant.

Conclusion: To the best of our knowledge, this is the first study on IDet treatment in patients with GDM. By our preliminary study, IDet is a viable treatment option in women with GDM. Further large prospective studies are needed to determine the efficacy and safety of IDet in GDM patients.

The Influence of Metformin Treatment on Total Cobalamin Levels and Active Cobalamin Levels in Hospitalized Type 2 Diabetes Patients

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Background and Objective: Long-term and high-dose treatment with metformin is known to be associated with cobalamin (vitamin B12, total cobalamin) deficiency in patients with type 2 diabetes. However it has been suggested that only the level of total cobalamin is low and not the transcobalamin attached cobalamin (active cobalamin or holotranscobalamin). In the Galilee Medical Center, active cobalamin is measured routinely when total cobalamin level is in the low normal range, less than 250 pg/ml (normal range 211-946 pg/ml). The purpose of this study was to investigate the influence of metformin treatment on total cobalamin and active cobalamin levels in hospitalized T2DM patients with low cobalamin levels.

Methods: Total cobalamin and active cobalamin levels were retrospectively analyzed in T2DM patients with and without metformin treatment, and in non diabetic patients. The inclusion criteria: hospitalization during the years 2012-2014 and age 40-80 years. Exclusion criteria: renal failure (GFR below 50), cobalamin treatment, gastrointestinal disease and drugs that significantly influence cobalamin absorption.

Results: Total cobalamin and active cobalamin levels were measured in 278 patients who meet the study criteria. 38 patients were excluded because of very low cobalamin levels (less than 150 pg/ml) due to accuracy concern. The exclusion allows the demonstration of linear association between total cobalamin and active cobalamin. The final sample includes 240 patients, 138 (57.5%) without diabetes, 80 (33.3 %) metformin-treated diabetic patients and 22 (9.2 %) non metformin treated diabetic patients.

There were no differences in the mean total cobalmin levels in all the groups, non-diabetics 201.5±25.4 pg/ml , diabetes with metformin 200.4±24.2 pg/ml and diabetes without metformin 200.5 ±25.3 pg/ml. Diabetes was associated with higher level of active cobalamin 39.2 ±21 pg/ml compare to non diabetic patients 32.8±16.2 pg/ml (P=0.005), although the diabetic patients were much older. Among the diabetic patients, metformin treatment was associated with lower level of active cobalamin 37.2 ±19.9 pg/ml compare to non metformin treated patients 46.7 ±23.8 (P=0.03). There were no differences in the age and sex of the patients in the two diabetic patients groups. Comparison Linear regression model between diabetic patients and non diabetic patients has demonstrated that the active cobalamin level is influenced mostly by the total cobalamin level (Standardized Coefficient Beta, STB=0.296) and less by the diabetes (STB=0.176).

Conclusion: In hospitalized type 2 patients, metformin treatment is associated with lower active cobalamin level but not total cobalamin.

The Association Between Glucose Variability and Mortality in Non-Critically Ill Hospitalized Patients in The Galilee Medical Center

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Background and Objective: In vitro and human studies suggest that increased glucose variability (GV) lead to greater oxidative stress. Studies of critically ill patients have consistently demonstrated that increased GV is independently associated with higher mortality. In non-critical ill patients the association of GV and mortality is controversial. The purpose of this study was there fore to investigate the association between GV and 90-day mortality in non-critically ill hospitalized patients.

Methods: This study retrospectively analyzed admissions to general medical departments during the first half of the year 2014. Patients with point-of-care glucose monitoring with or without diabetes were selected.

Results: There were 4,421 admissions to the general medical departments with at list one point-of-care glucose monitoring. After applying the next criteria: a minimum of four glucose values per hospitalization, age 18-85 and length of hospitalization $\leq$ 10 days, the sample consisted of 2123 hospital admissions with 25,143 blood glucose tests. Death within 90 days from admission occurred in 142 cases (6.7%). There was no association between glucose variability and 90 days all-cause mortality after examination with standard deviation (Logistic regression, P=0.198) and glucose measurements range (Logistic regression, P=0.126) with adjustment for age and sex.

In the next step more criteria were applied including: age 80 or less years, admission directly to general medical departments, excluding patients that were transferred to surgical or intensive care departments. After the criteria were applied, the final sample consisted of 1575 admissions with 19,727 blood glucose tests. Death within 90 days from admission occurred in 73 cases (4.6%). Also in this more homogenous group, there was no association between glucose variability and mortality after examination with standard deviation (Logistic regression, P=0.365) and glucose measurements range (Logistic regression, P=0.163) with adjustment for age and sex.

108 patients (6.9%) were without diabetes diagnosis. There was no different in 90 day mortality between patients with and without diabetes (P=0.339).

Conclusions: Our study showed that glucose variability (measure by standard deviation and Range) is not associated with 90-days all-cause mortality in non-critically ill patients with point-of-care glucose monitoring.

The Effect of Military Service on Metabolic Control, Weight Status and Incidence of Acute Diabetes Complications in Young Adults with Type 1 Diabetes

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Objective: To evaluate the effect of military service on metabolic control and incidence of acute diabetes complications.

Research Design & Methods: Clinical and laboratory data of 145 T1D patients born between 1988-1992 and followed at the National Center of Childhood Diabetes was retrieved from medical records. The study group included 76 [36 males (47.4%)] T1D conscript volunteers and 69 [38 males (55.1%)] T1D non-volunteers served as controls. Outcome measures: HbA1c, BMI-SDS, insulin dosage, occurrence of severe hypoglycemia or diabetic ketoacidosis.

Results: Metabolic control was comparable in volunteers and non-volunteer controls [mean HbA1c (one year prior to enlistment 7.83±1.52% vs. 8.07%±1.63; at enlistment 7.89±1.36% vs. 7.93±1.42%; one year after enlistment 7.81±1.28% vs. 8.00±1.22%; two years after enlistment 7.68±0.88% vs. 7.82±1.33% and 3 years after enlistment 7.62±0.80% vs. 7.79±1.19%)]; with no significant changes from baseline throughout follow-up. BMI status and insulin requirements were similar and remained unchanged in volunteers and controls [mean BMI-SDS (one year prior 0.23±0.83 vs. 0.29±0.95; at enlistment 0.19±0.87 vs. 0.25±0.98; one year after 0.25±0.82 vs. 0.20±0.96; two years after 0.10±0.86 vs. 0.15±0.94 and 3 years after enlistment 0.20±0.87 vs. 0.16±0.96) and mean insulin dose in U/kg/d (one year prior 0.90±0.23 vs 0.90±0.37, at enlistment 0.90±0.28 vs 0.93±0.33, one year after 0.86±0.24 vs 0.95± 0.33, two years after 0.86±0.21 vs 0.86±0.29 and 3 years after 0.87±0.23 vs 0.86±0.28)]. There were no severe hypoglycemia episodes and DKA events in both groups.

Conclusions: Our data suggests that young adults with T1D can maintain similar metabolic control to those who choose not to serve in the army, without significant weight change or severe acute diabetic complications.

The Effect of Vitamin D Supplementation Metabolic Parameters and Arterial Stiffness in Diabetic Patients

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Vitamin D insufficiency and deficiency (serum level of 25-hydroxyvitamin D below 30ng/ml or 20 ng/ml, respectively) has been recognized as a worldwide pandemic. Evidence suggests that vitamin D is lacking in various nonskeletal conditions such as cardiovascular disease, hypertension, diabetes, cancer, and autoimmune disorders among others. However, it is unclear whether correcting vitamin D levels is beneficial. The aim of this study was to compare the effect of vitamin D supplementation to placebo on different metabolic parameters and arterial-stiffness in diabetic patients with vitamin D insufficiency or deficiency.

In this prospective, randomized, double blind study 44 diabetic patients with vitamin D insufficiency or deficiency were randomly assigned to receive vitamin D3; n=20 (2000 IU daily for insufficient state and 4000 IU daily for deficient state) or placebo; n=24 (the same dosage of olive oil), for 3 months. BMI and waist circumference, fasting glucose, HBA1C,lipids, hsCRP, blood pressure monitor and Arterial-stiffness expressed as augmentation index (Aix) were measured at baseline and after 3 months of treatment.

The mean change from baseline of vitamin D level (25OHD) was significantly greater in the treatment group. There was no change in fasting glucose, HBA1C and hsCRP in either group compared to baseline. Triglycerides were significantly increased with vitamin D treatment compared to placebo (mean change from baseline after log transformation +0.15±0.3 vs. -0.11±0.3, respectively, p=0.008). There was no significant change in LDL or HDL compared to base line in both groups .BMI decreased in both groups but less with vitamin D (mean change from baseline -0.1±0.54 with vitamin D vs. -0.44±0.66 with placebo p=0.073). There was no change in blood pressure monitor or AIx compared to baseline in either group.

Vitamin-D supplementation did not effect metabolic and inflammatory parameters in diabetes patients lacking vitamin D. Blood pressure and arterial-stiffness did not change as well. This data questions the benefit of vitamin D correction.

Use of Basal – Bolus Insulin Protocol in Diabetic Patients Treated with Glucocorticoids in Internal Medicine Department: A Retrospective Cohort Study

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Background: Despite the recognized benefits of basal-bolus insulin protocols in diabetic inpatients, the data about using basal- bolus regimen in hospitalized diabetic patients treated with glucocorticoids is limited.

Methods: We conducted a retrospective cohort study that examined the difference in glycemic control between hospitalized diabetic patients with and without glucocorticoids treatment. All patients were treated with basal-bolus regimen and had elevated inflammatory markers. The electronic charts of diabetic patients admitted in 2013-2014 were reviewed. For each patient, the average glucose levels at 8:00AM, 12:00AM, 5:00PM and 8:00PM were calculated. , The former group included 67 patients and the control group included 99 patients.

Results: The sample included 166 diabetic patients, where 67 of them, received glucocorticoids treatment. There were no significant differences between patients with and without glucocorticoids treatment in demographic characteristics (age: 70.5±11.8 vs 68.18±11.9; BMI: 29.6 ±5.12 vs 29.6±7.07; length of admission: 15±16 vs 16.1± 15.9, respectively) and inflammatory markers and glycemic control (HBA1C: 8.47±1.86% vs 8.6±1.9%; CRP value: 137.8±92 vs 142.2±106.29, respectively). Mean daily glucose was higher in patients taking glucocorticoids (225.4 ±48.01 vs 196.5±43.8, P<.0001), and was significantly higher at 5:00PM (241.4±62.44 vs 183±53.14, P<.0001) and 8:00PM (253.7±72.6 vs 197.9±53.77). The patients in control group received higher dosage of basal insulin (18.45 ±8.27 vs 11.47±5.81) without significant differences in prandial insulin doses.

Conclusions: Diabetic patients treated with glucocorticoids had significantly higher mean blood glucose due to elevation of blood glucose in the afternoon and evening. They received lesser doses of basal insulin and the same doses of prandial insulin. Overall the two groups had insufficient blood glucose control.

Lower Basal Insulin Dose - Better Control in Type 1 Diabetes

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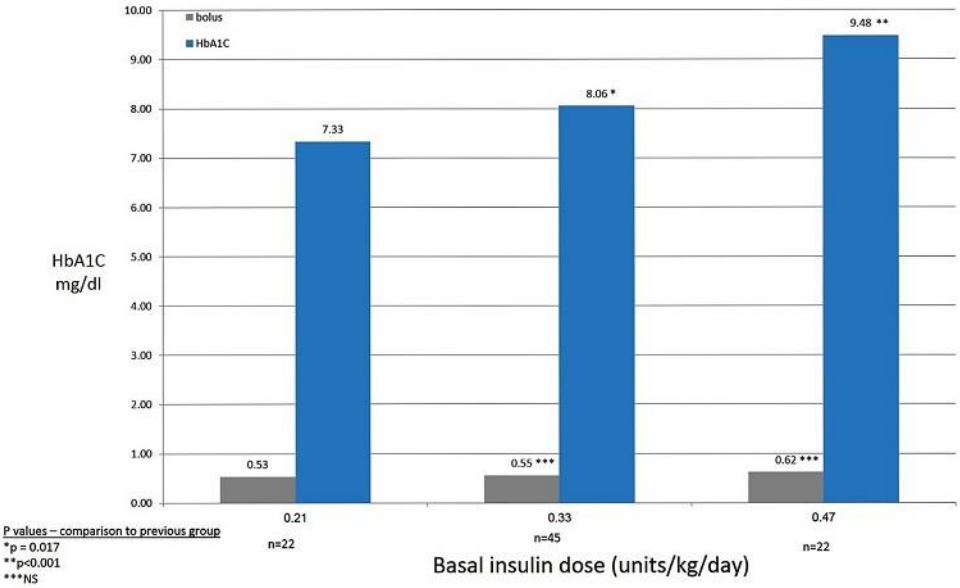
Introduction: There is no valid evidenced-based recommendation for the optimum basal insulin dose in Type-1 Diabetes Mellitus when supplied either by continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI). We studied this previously by evaluating the dose associated with successful fasting. Another way of looking at this is by evaluating the association between basal insulin dose and HbA1c. To this end we performed a retrospective study of 89 children and young adults with T1DM.

Patients and Methods: 89 (mean age 14.67±4.8 years (range 3-29)) patients were enrolled. 46 were treated with CSII and 43 with MDI (glargine as basal insulin). Basal insulin used was either downloaded from the insulin pump or taken as the dose registered in the chart. Glucose data were downloaded from patients' glucometers. Mean time between data download and HbA1c determination was 0.9 ± 0.78 months. We divided the patients by quartiles according to basal insulin dose and determined the average HbA1c for each quartile. The second and third quartiles were joined and are presented together in the graph.

Results: Optimal HbA1c occurs when basal insulin dose of 0.21 units/kg/day is used.



Conclusion: With lower basal insulin levels lower HbA1C was achieved despite the same total bolus dose. The optimal basal dose as determined by this study is the same as shown for fasting individuals of similar age.

Metformin Does Not Increase Lactate Level in Patients Admitted to Internal Ward

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Metformin, an anti-hyperglycemic drug, is contraindicated in various conditions due to concerns about the rare adverse event of metformin-associated lactic acidosis (MALA). MALA is thought to develop in acute illness (e.g. hypoxia, acute hypoperfusion). Recent data suggests that the rate of MALA does not differ in those treated with metformin versus other anti-hyperglycemic agents, and that expansion of metformin use is needed. The aim of this study was to evaluate lactate level in acute setting, during the first day of admission to an internal-medicine ward. A total of 140 patients participated in the study, 54 diabetic patients on chronic metformin treatment, 33 diabetic patients without metformin and 53 patients with no diabetes. Average Lactate and pH levels were comparable between the three groups and did not differ in different eGFR levels. No patient was hospitalized for lactic acidosis as the main diagnosis.

These results suggest that chronic metformin treatment does not cause hyper-lactatemia in acute illness; during the first day of hospitalization in an internal-medicine ward. This data supports the expansion of metformin use.

Clinical Characteristics and Disease Outcome of Patients with Nonmedullary Thyroid Cancer and Brain Metastases

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Background: Brain metastases reportedly occur in ~1% of cases of nonmedullary thyroid cancer (NMTC). Their optimal management and outcome are unclear. This study sought to evaluate the clinicopathological characteristics and survival of patients with NMTC and brain metastases.

Methods: The Rabin Medical Center Thyroid Cancer Registry covering the period from 1962 through 2014 was searched for all patients with NMTC and distant metastases. Those with brain metastases were identified, and data on clinicopathological characteristics, disease course, treatment, and outcome were collected from their medical files.

Results: Of 134 patients with NMTC and distant metastases, 8 (5.9%) had brain metastases. Mean age at initial diagnosis was 45.5±16 years. Initial treatment included total thyroidectomy and radioiodine therapy (initial dose 175 MCI, cumulative dose 473 MCI). Histologically, 5 patients had papillary type (1 classical, 3 follicular variant, 1 tall cell) and 3, poorly differentiated carcinoma. Mean interval from primary diagnosis to brain metastasis was 71.5 months (range 0-207). All patients had lung metastases, either proceeding (n=7) or synchronous with (n=1) the brain metastases, and 6 (75%) had bone metastases. Macroscopic (≥ 1 cm) lesions were found in 6 patients, bilateral in 4. Surgery was performed in 4 patients and radiotherapy in 7; 3 patients received tyrosine kinase inhibitors. Median overall survival (OS) time after diagnosis of brain metastases was 23 months (range 2-300). OS rates were 75% at 1 year and 50% at 2 years. An unusual 25-year survival was observed in one patient with brain metastases at initial diagnosis.

Conclusions: Brain metastases can be expected in up to 6% of patients with NMTC and distant metastases and are highly associated with lung metastases. Some patients show an indolent evolution with >2-year OS , supporting the use of aggressive treatment. Systematic screening for brain metastases should be considered for all patients with NMTC and lung and bone metastases.

Clinical and Pathological Aspects of Amyloid Goiter in a Patient With Familial Mediterranean Fever

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A 56-year-old male with Familial Mediterranean Fever (FMF), not adherent with Colchicine treatment, was evaluated for severe weight loss and anemia. A CT scan demonstrated a large goiter. Thyroid function tests were normal and fine needle aspiration was suggestive of a benign adenomatoid nodule. The patient was referred to a total thyroidectomy because of compression symptoms. Pathology evaluation found a huge thyroid gland with fatty metaplasia. The diagnosis of amyloid goiter was established using Congo red staining. Following the operation the patient remain severely hypothyroid despite of high doses of oral levothyroxine, as part of malabsorption syndrome. Normalization of TSH level became possible only while using intramuscular Levothyroxine (off- label use).

Amyloidosis results from the deposition of amyloid proteins in the extracellular spaces of tissues. FMF is a common cause of secondary amyloidosis. The most common clinical manifestation of FMF-related amyloid is the development of proteinuria and eventually, end stage kidney disease. Amyloid goiter due to amyloid deposition in the thyroid gland is rare. It commonly presents as a rapidly growing neck mass causing compression symptoms. The diagnosis should be considered in any patient with systemic amyloidosis presenting with a large goiter and euthyroid state. Definitive diagnosis is made by histologic evaluation of the resected thyroid gland. Amyloid material infiltrates the parenchyma, distorting the normal tissue architecture and showing fatty metaplasia. Histochemical staining with Congo red confirms the diagnosis.

Among patients with systemic amyloidosis, histological involvement of the gastrointestinal tract is common though often subclinical. Although the presence of GI symptoms varies between patients, malabsorption is one of the most clinically important.

FMF is a common disease in Israel, and although rare, an amyloid goiter may be part of the clinical presentation. This case demonstrates the clinical and pathological aspects of this unusual cause of thyroid goiter.

A Cohort of 134 Patients with Differentiated Thyroid Cancer and Distant Metastases Treated at a Single Tertiary Medical Center in Israel

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Introduction: Cervical lymph node metastases (LNM) is a strong predictor for persistent disease; however, the poorest prognosis in differentiated thyroid cancer (DTC) is associated with distant metastases (DM) and/or extensive local invasion.

Aims: To investigate factors associated with improved outcome in DTC patients with DM.

Methods: From the Rabin Medical Center Thyroid Cancer Registry we identified 134 patients with DTC and DM operated during 1970-2014, having sufficient data for analysis. Anaplastic cancer was excluded. Data on clinical characteristics, treatment modalities and disease outcome were obtained from medical records. Most patients were treated with total thyroidectomy and I-131, TKIs were given to 15 patients. Median follow-up was 9 yrs.

Results: Age at diagnosis was 58.8±18, 60% were females, primary tumor size was 33.1±26 mm, 57% were T3T4, 51.3% had extrathyroidal extension (ETE) and 53.2% had LNM. Histopathology was PTC/PTCFV 70%, FTC 10.5% and intermediate differentiated 19.5%. In 53% DM was synchronous (M1). Cumulative I-131 dose was 404 ± 245 mCi. Outcome at last follow-up was: resolved 28.4%, improved/stable 28.4% and progressive 43%. The overall survival was 65.7%. Disease progression was higher for metachronous (53% vs 34%) and intermediate type (64% vs 46% FTC and 34% PTC). Site distribution was: lung-only 77, bone-only 17, lungs and bones 35, brain 9 liver 4 uterus 1. Compared to all patients with bones metastases, those with lung-only were older (48 vs 59 yrs) more female (63 vs 51%) had smaller primary (29 vs 36 mm) more PTC/PTCFV type (80 vs 47%) and less disease progression (21 vs 42%).

Conclusion: There is a wide spectrum of clinical characteristics in thyroid cancer patients with distant metastases that can be used to predict disease outcome. Factors associated with better outcome are more differentiated cancer, synchronous DM and lung-only disease.

Spuriously Elevated Free T4 in Conjunction with Elevated TSH: a Case Report, the Proposed Mechanism, and a Suggestion for a Simple Confirmatory Test

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A 40 year old female with Hashimoto Thyroiditis hypothyroidism and low adherence to treatment was referred due to a significant increase in free T4 levels in parallel with elevated TSH. Clinically, she did not present symptoms or signs of thyrotoxicosis. The presence of anti-T4 antibodies was suspected and was evaluated using two different techniques: A standard two-step competitive assay and a novel technique involving mixing studies of the patient`s serum and normal serum with the appearance of the same abnormality in the normal serum.

The main differential diagnosis of an elevated TSH yet elevated free T4 include: a laboratory artifact; fluctuating adherence to replacement therapy; a pituitary adenoma producing TSH; and Thyroid hormone resistance.

The production of antibodies against thyroid hormones is usually secondary to damage of the thyroid tissue with the exposure of neo-epitopes containing tyrosine residues bound to iodine molecules. This disturbance has no clinical relevance. This laboratory abnormality results from binding of these antibodies to the reagent used to test for free thyroid hormones. This reagent contains T4-like molecules that are capable of producing fluorescence that compete with the patient`s T4 for the laboratory kit binding sites. Therefore, the binding of the antibodies to the reagent, prevents it`s binding, leading to a minimal fluorescent reaction and vis-à-vis, to a falsely increased free T4.

This case highlights the difficulties in evaluating such patients due to the interference involved in the laboratory technique commonly used in Israel and other countries. In this work, we also present a new yet simple confirmatory test to be used when such interference is suspected.

Treatment of Resistance to Thyroid Hormone in Pregnancy: How to Address the Challenge?

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Background: Resistance to thyroid hormone (RTH) is a syndrome characterized by reduced end-organ responsiveness to thyroid hormones. Most patients with RTH are clinically euthyroid. Thus, antithyroid treatment is unnecessary. However, the approach in RTH patients during the pregnancy remains challenging and is based on the fetus genotype.

Methods: Herein, we describe 28-year-old woman which was referred to endocrinology clinic for the evaluation of goiter, tachycardia and poor weight gain at the age of 9. Her thyroid function tests were: FT4- 4.85 ng/dl (normal range 0.6-1.8), TT3 was 363 ng/dl (normal range 80-180), TSH was 1.1 mU/l (normal range 0.2-3.8). Radioactive iodine uptake test with I131 revealed high uptake (42% and 84% at 2 and 24 hours respectively. Under PTU treatment for presumed hyperthyroidism she has increased goiter size with elevated TSH levels, FT4 and TT3 levels were high despite the treatment. RTH was suspected and genetic tests of proposita were performed. The proposita was found de novo mutation in exon 10 of the TR ß gene. At the age 26 she was married and underwent additional genetic counseling in order to assess likelihood of the same condition in her progeny. In addition to mutation in exon10 c.1357C>A; p.P453T, SNP c.735C>T; p.F245F in a heterozygouse state was detected. Genetic testing of fetus performed by amniocentesis did not reveal the mutation p.P453T. She was treated with PTU 450 mg daily during the pregnancy in order to prevent catabolic state in fetal life and suppressed TSH at birth.

Conclusion: RTH is rare condition. The mainstay in the management of RTH patients is to recognize the correct diagnosis and avoid unnecessary treatment. In pregnant mothers with RTH, treatment with PTU can be beneficial for growing fetus. Significance of single nuclear polymorphism in our patient needs to further investigation.

A Natural Experiment in Mass Media Modulated Pharmacokinetics After a Change in Tablet Formulation

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Background: After a new formulation of levothyroxine was distributed in Israel, side effects were reported to the Ministry of Health generating extensive media coverage. The purpose of this study was to determine whether the new formulation was associated with a change in thyroid-stimulating hormone (TSH) levels of treated patients
and to evaluate the effect of the extensive media coverage on the incidence of laboratory test performance.
Study Design: Retrospective-cohort and crosssectional analysis.
Methods: All patients from the Leumit Health Services of Israel treated with levothyroxine between October 2009 and February 2012 were included in the study. A retrospective cohort was constructed of patients treated and maintained within the desired target range (0.35-5 mIU/L) from January to July 2010. A longitudinal analysis was conducted to calculate the monthly distribution of TSH levels from laboratory tests during routine care over 26 months. Data were stratified by cohort and noncohort patients.
Results: Data were captured for 18,106 levothyroxine-treated patients; 1140 were included into the retrospective cohort. In both subpopulations a sharp rise in the number of tests performed monthly is observed at the peak of media coverage during October and November 2011. In the retrospective cohort the proportion of TSH results within target range fell to a low of 67.5% during December 2011, with 25.3% between 5.01 and 20
mIU/L. Results 20 mIU/L then peaked at 3.8%indicating an increase in patients who stopped taking levothyroxine.
Conclusions: These results demonstrate the power of mass media to influence patient behavior and to foment a public health scare.

Infantile Consumption of Soy- Based Formula is not Associated with Early onset of Puberty and Overweight in School- Age Children

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Background Children in industrialized and developing countries have a higher tendency to present earlier signs of puberty. One hypothesis includes the hormonal effects of phytoestrogens found in soy products.

Objective to examine the association between consumption of soy-based food in early infancy and childhood and the incidence of early or precocious puberty and overweight in school-aged children.

Methods the study population for this case control study was randomized from a prospectively followed cohort of all babies born at Assaf Haroffeh Medical Center and followed for milk allergy signs and food intake until the age of 3 years (A nested cohort). It was divided to those who were allergic to milk, and thus consumed only soy-based formula and food during infancy and childhood (soy group) and a randomized control group who consumed a non-soy based formula . For both groups, food habits data were available during infancy and collected from 3 days food diaries during the current study. Physical examination, including weight, height, blood pressure and Tanner Pubertal Staging were performed.

Results Study population included 89 participants, 29 in the soy group. Mean age was 8.5±0.64 years, 45 males. There was no association between soy consumption in infancy and early or precocious puberty and overweight.

Conclusions This is the first prospective long term follow up study of a milk allergy proven cohort and a randomized control group, indicating there is no association between infantile soy consumption and signs of early or precocious puberty, and overweight.

Clinical Management of Children and Adolescents with Gender Dysphoria in Israel

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Objective: To describe characteristics at presentation and treatment of children and adolescents with gender dysphoria in Israel.

Methods: A retrospective chart review of 23 children and adolescents (< 18 years) with the diagnosis of gender dysphoria followed at a tertiary children hospital from February 2013 to December 2015.

Results: Of the 23 patients, 4 (17%) identified as female-to-male (FtM), 19 (83%) as male-to-female (MtF). The gender dysphoria population increased since the establishment of the clinic from 1-2 new referrals to 10 new referrals per 6 months. Median age at referral was 15.25 years (range 4.58-17.66 years). At time of referral, 78% have completed their sexual maturation in their biological gender. Gonadotropin-releasing hormone analog treatment was initiated in 19 (83%) patients at a mean age of 15.6±1.5 years. Cross-sex hormones were initiated in 12 (52%) patients at a mean age of 16.7±1.0 years. No severe side effects were recorded in patients treated with Gonadotropin-releasing hormone analog and testosterone or estrogen. One MtF patient underwent genital sex reassignment surgery at age 18.16 years. One FtM patient underwent mastectomy at age 18.25 years.

Conclusion: After establishment of a multidisciplinary childhood and adolescent gender dysphoria clinic, referral rate to the clinic increased fivefold. Treatment with gonadotropin-releasing hormone analog and/or cross-sex hormones, in collaboration with transgender-competent mental health professionals, is an intervention that appears to be appropriate in carefully selected youth with gender dysphoria. Long-term follow-up studies are needed to determine the safety and efficiency of these treatments in this age group.

Growth and Pubertal Patterns in Young Survivors of Acute Lymphoblastic Leukemia

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Background: Childhood acute lymphoblastic leukemia (ALL) survivors are at increased risk for endocrine late effects.

Aims: The aims were to evaluate growth and pubertal patterns in patients diagnosed with childhood-ALL and to identify risk factors for impaired growth and puberty.

Methods: Longitudinal assessment of anthropometric measurements and pubertal status of 183 childhood-ALL survivors [154 chemotherapy-treated and 29 chemotherapy+cranial radiation-treated; mean age at therapy 6.26±3.8 years and 6.5±4.34 years, respectively] were retrospectively extracted from medical files. Included in the study were patients aged 8-30 years at data collection, disease-free>one year, who remained in first remission, with follow-up≥3 years.

Results: Median age at last endocrine visit was 16.1 years (range 8.2-27.6 years); median duration of follow-up from diagnosis was 8.7 years (range 3-21.4 years). Mean age at pubertal onset was normal (girls:10.3±1.3 years; boys:12.0±1.3 years); precocious puberty was diagnosed in 8.7% of patients.

Obesity and overweight were found in 9.3% and 22.9% of the cohort, respectively. Patients treated with chemotherapy+cranial radiation as compared to chemotherapy-alone were shorter (mean height-SDS -0.93±0.92 vs. -0.21±1.1, *P*=0.001), had higher prevalence of adult short stature (13% vs. 2.2%) and had a higher rate of precocious puberty in girls (30% vs. 9.4%) with no difference in age at menarche.

Predictors for occurrence of endocrine disorders included: female gender (OR 3.26, 95% CI 1.04–10.1), cranial irradiation treatment (OR 3.96, 95% CI 1.14-13.78) and younger age at diagnosis (OR 0.83, 95% CI 0.68-1.02). Predictors for obesity - a higher BMI-SDS at diagnosis (OR 1.46, 95% CI 1.18-1.81), and for short stature - lower height-SDS at diagnosis (OR 0.35, 95% CI 0.13- 0.94).

Conclusions: Our findings suggest that although most patients treated with chemotherapy-alone attained normal adult height and puberty, those treated with adjuvant cranial irradiation were at increased risk for short stature. Childhood ALL survivors were at an increased risk for overweight and obesity.

Therefore, clinicians need to screen for metabolic disorders early in survivorship, and nutritional intervention and physical activity should be introduced during cancer treatment.

Vandetanib Induces a Significant Anti-tumor Effect in Metastatic Medullary Thyroid Carcinoma with Ectopic Cushing Syndrome: Case Report and Review of the Literature

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Background: Ectopic Cushing's syndrome (ECS) due to ACTH-producing MTC is an uncommon event with a poor prognosis. Control of hypercortisolism with inhibitors of steroidogenesis or ACTH secretion is often unsuccessful. Vandetanib, a tyrosine-kinase inhibitor selectively targeting the RET, EGFR and VEGFR receptors, has demonstrated an anti-secretory effect in a few case reports; however, to date, no tumor size reduction has been reported in MTC-related ECS patients treated with vandetanib.

Aim: We report the anti-tumor effect induced by vandetanib in a patient with metastatic MTC that developed ECS in parallel with tumor progression.

Results: A 55 year-old woman diagnosed with sporadic MTC underwent total thyroidectomy 20 years ago. During follow-up, multiple foci of metastatic disease were noted in the neck and mediastinal lymph nodes, in the lungs and in the bones; however, the disease was characterized by an indolent course for years, without significant symptoms. During a routine follow-up visit two years ago, findings suggestive of Cushing syndrome were observed on physical examination. The biochemical evaluation demonstrated a severe elevation in calcitonin levels, lack of cortisol suppression after an overnight 1 mg dexamethasone suppression test, lack of cortisol and ACTH suppression after 8 mg IV dexamethasone, elevated plasma ACTH levels, and elevated 24 hours urinary free cortisol levels. A pituitary MRI was negative, and an IPSS was compatible with ECS. Treatment with vandetanib at a dosage of 200 mg/day was commenced. The patient showed a significant, rapid and consistent improvement, in parallel with a decrease in tumor size as demonstrated on follow-up CT.

Conclusion: Our report demonstrates that vandetanib may effectively control the signs and symptoms related to ectopic ACTH secretion in patients with advanced progressive MTC and that it is also effective in decreasing tumor size and inducing tumor-control. Further studies are needed to confirm the possible anti-tumor effect of vandetanib in other neuroendocrine tumor-related ECS.

Role of An Inpatient Endocrine Consult Service at a Referral Medical Center in Israel: Preliminary Analysis of Treatment and Outcome Effects at the Tel Aviv-Sourasky Medical Center (TLVMC)

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Background: Endocrinology-metabolism is increasingly viewed as an ambulatory care subspecialty. No published data exists on the scope and role of an endocrine inpatient service in the modern era.

Structure and Working Frame: At TLVMC, consults are requested through a computerized system and are initially addressed by endocrine fellows and then supported by a four tier system: endocrine specialist; head of the endocrine consult service [EO]; endocrine subspecialists recruited as needed; formal and informal departmental and inter-departmental clinical case conferences.

Methods: We analyzed our inpatient service reports from April 1, to may14, 2015.

Results: We received 388 consult requests. Fifty consults requested exclusively to assist with the control of glycemia were excluded from this analysis, thus leaving "non-glucocentric" 338 consults in 147 patients for this evaluation. Calls were nearly evenly split between medicine and surgical wards [48%; 52%, respectively]. Mean patient age was 602± yrs with a female gender preponderance [61%]; mean response time was 4.2±2.8 h; number of consultations per patient - 2.3 ±3.3. Case distribution was as follows: thyroid 47%; calcium/bone 12 %; adrenal 11%; pituitary 9.5%; electrolyte imbalance-3.4%; hypertension-6.1%; diabetes-7.4%; pancreatic tumors-1.4%; other-2%. Consult-induced changes were noted in treatment (42.2%); diagnosis (5.4%); results of treatment (4.8%) and post hospitalization treatment (2.7%). Significant correlation existed between disease severity and the number of consultations/patient [$R=0.22$ ($P<0.05$)] and the number of consultations vs. the effect of the consult-driven intervention ($R=0.29$ ($P<0.05$).

Conclusion: To our knowledge this is the first report on an organized endocrine inpatient consult service in current medicine. The results support the concept that such service is vital for inpatients: it modifies the clinical course in more than 50% of cases and achieves a post admission carry over effect. Such analysis also provides tools towards better understanding of the scope, needs and impact of inpatient endocrine care.

Hyperglycemia Affects the Pituitary Gonadotrope Epigenome

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The connection between metabolic state and reproductive competence is complex and not yet fully understood. Although much of the input on the metabolic state is received at the hypothalamus and translated into changes in GnRH synthesis and release, we hypothesized that the pituitary gonadotropes are also sensitive to high glucose levels, and may thus be affected directly in states of hyperglycemia to impart some of the effects on reproductive function. We found that the gonadotropes indeed express predominantly the insulin-independent glucose transporter, Glut-1, and incubation of gonadotrope cell lines is followed by increased glucose metabolism, as well as increased expression of the glucose responsive *Txnip* gene. The resulting drop in NAD+ and increase in alpha-ketoglutarate availability would likely alter the activity of enzymes requiring these as cofactors. These include the Sirtuin histone deacetylases which repress gene transcription, and the JmjD histone demethylases and Tet DNA hydroxymethylases/ demethylases which increase transcription. Indeed gonadotropes cultured in high glucose showed elevated global levels of histone acetylation and H3K4 trimethylation, as well as global reduction in DNA methylation and an increase in hydroxymeythylation, all of which are associated with increased gene expression. Transcriptome analysis confirmed that expression of a large number of genes in these cells is increased after incubation in high glucose, including many encoding chromatin modifying enzymes, as well as Sirtuin substrates, and various genes in the Wnt signaling pathway. Expression of the gonadotropin genes was also affected, most notably for *Fshb* which was clearly repressed in high glucose conditions. The return of cells to normal glucose restored expression of some of the genes, such as *Txnip*, but *Fshb* levels remained low and the affected chromatin modifications were not reversed. Our findings suggest that hyperglycemia aberrantly affects the gonadotrope epigenome with potentially long-term effects on gene expression and thus also reproductive function.

GnRH Induces Blebs Formation in the Gonadotrope LβT2 Cells; Members of a GnRH Receptor Associated Signalosome are Recruited to the Blebs

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We have previously described a multi-protein signaling complex (signalosome) associated with the GnRH receptor (GnRHR). We now report that GnRH induces blebs formation in the gonadotrope LβT2 cells. The blebs appear within ~2 min at a turnover rate of ~2-3 blebs/min and last for at least 90 min. Formation of the blebs requires active ERK1/2 and RhoA-ROCK but not active c-Src. Although the following ligands: EGF>GnRH>PMA> cAMP stimulate ERK1/2 in LβT2 cells, they produced little or no effect on blebs formation as compared to the robust effect of GnRH (GnRH>PMA>cAMP>EGF), indicating that ERK1/2 is required but not sufficient for blebs formation possibly due to compartmentalization of ERK1/2. Members of the above mentioned signalosome are recruited to the blebs, some during bleb formation (GnRHR, c-Src, ERK1/2, FAK, paxillin, caveolin-1 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. GnRH induces blebs in primary cultures of rat pituitary cells and isolated mouse gonadotropes. Since the signalosome is thought to be involved in cell migration, it is possible that the blebs play a role in this process.

Clinical and Hormonal Features of a Male with Selective Follicule-Stimulating Hormone (FSH) Deficiency

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Introduction: Gonadotropins (LH and FSH) regulate the production of sex steroids and are crucial for the pubertal development and fertility. There are several genetic defects that cause hypogonadism at different levels. Inactivating mutations in the FSHß gene are rare causes of delayed puberty and infertility. In women it will cause impaired sexual maturation and fertility while in men it will cause infertility.

Case Description: A 29 yo male was evaluated due to primary infertility and a low sperm count. He had normal sexual development and function. At his first evaluation at the age of 24 he had an undetectable FSH and normal LH and testosterone with a normal MRI of the pituitary gland. He was treated with Menogon (LH and FSH) for 7 months and fathered two children. He was recently referred to our center due to infertility. Basal and stimulated LH were normal (1.8 IU/l and 11.6 IU/l) while FSH levels were undetectable and rised suboptimally (

Conclusion: FSH deficiency is a rare cause of infertility in men that can be easily treated when fertility is desired.

Mega-Giant Prolactinomas: a Large Cohort of Massive and Aggressive Pituitary Adenomas

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Objectives: Prolactin (PRL)-secreting macroadenomas usually measure between 10-40 mm in maximal diameter and typically are well-controlled medically. Giant (adenoma size 40 mm) PRL-tumors are not common, and mega-giant prolactinomas (adenoma diameter 60 mm) are extremely rare, and their management outcomes have not been well characterized.

Design & Methods: We have identified 18 subjects (16 men, 2 females) with mega-giant adenomas (adenoma size 60 mm; PRL 1,000 ng/ml) in five pituitary centers and summarized their clinical characteristics and response to treatment.

Results: Mean age at diagnosis was 36.3±13.5 years (range, 12-59 years). Mean adenoma size was 71.8±10.2 mm (range, 60-92 mm). Main complaints included headaches in 11 patients, visual deterioration in 9 subjects, decreased libido or erectile dysfunction in 9 males, and behavioral changes in two. Fourteen patients (78%) had visual fields damage, mostly bitemporal hemianopsia. Mean serum PRL at presentation was 28,465 ng/ml (range, 1,300-270,000). All patients were treated with cabergoline (mean dose, 3.9±2.0 mg/week), besides one that was given bromocriptine. Treatment with dopamine agonists achieved PRL normalization in 11/18 patients with a mean time interval of 67±87 months (median, 20 months) to normalization. Visual improvement occurred in 12/14 patients with pre-treatment visual damage. Nine patients underwent pituitary surgery (transsphenoidal, 7; transcranial, 2). None of the 6 patients whose PRL levels were elevated before surgery achieved hormonal remission post-operatively. Currently, after a mean follow-up of 7.8±5.1 years, 15/18 patients had significant adenoma shrinkage. Eleven patients are normoprolactinemic, 3 are partially controlled (PRL 3 x ULN), and 4 remained with significantly elevated PRL. Most patients reported disappearance or improvement of their complaints.

Conclusions: Mega-giant PRL-adenomas are invasive, uncontrolled by surgery, but respond fairly well to medical treatment. Long-term therapy with high dose cabergoline is the clue for their successful management, achieving biochemical and clinical remission in most patients.

Role of the Endocannabinoid/Cannabinoid-1 (CB1) Receptor System in Prader-Willi Syndrome

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Prader-Willi syndrome (PWS), a complex genetic disorder, is primarily characterized by childhood-onset hyperphagia and extreme obesity. While many studies have tried to identify the molecular mechanisms that lead to the development of obesity in PWS, no direct or indirect link has been established between either a genetic or hormonal dysfunction related to PWS. Among the numerous metabolic regulators, endocannabinoids (eCBs) are critically involved in the control of feeding, body weight, and metabolism, and globally-acting cannabinoid-1 (CB1) receptor antagonists (e.g. rimonabant) reverse obesity both in animals and humans. However, due to their neuropsychiatric side effects, they are no longer considered as a valid treatment for obesity in humans.

Using an established mouse model for obesity in PWS, *Magel2*-null mice, we measured the gene expression of CB1 receptor as well as the endogenous levels of the main eCBs, anandamide (AEA) and 2-arachidonoylglycerol (2-AG). We then determined the efficacy of the peripherally-restricted CB1 antagonist, JD5037, in treating obesity in female and male *Magel2*-null mice. To assess the relevance of our findings to humans, we measured eCB levels in the serum of individuals with PWS and their age- and gender-matched healthy controls.

Increased circulating levels of AEA and reduced CB1 receptor expression in adipose tissue were found in obese *Magel2*-null mice. Daily oral treatment of obese *Magel2*-null mice and their controls with JD5037 (3 mg/kg/d for 28 days) resulted in significant and comparable reductions in body weight, food intake and metabolic parameters in both mutant and control mice. Human patients with PWS showed increased levels of 2-AG, but not AEA.

In conclusion, dysregulation of the peripheral eCB/CB1 system may contribute to obesity in *Magel2*-null mice and humans with PWS. Our findings with JD5037 in *Magel2*-null mice may provide the rationale for clinical testing of peripherally-restricted CB1 receptor antagonists for the treatment of obesity in PWS.

Peroxisome Proliferator-Activated Receptor Alpha (PPARα) Plays an Important Role in the Attenuation of Fatty Liver by Cannabinoid-1 (CB1) Receptor Blockade

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The endocannabinoid (eCB) system is increasingly recognized as being of crucial importance in obesity-related metabolic complications, one of which is hepatic steatosis. eCBs, via the stimulation of hepatic cannabinoid-1 (CB1) receptors, increase *de novo* lipogenesis and inhibit fatty acid oxidation. CB1 receptor blockade reverses the high-fat diet (HFD)-induced hepatic steatosis, and upregulates the expression of the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα). Yet, the molecular mechanisms by which the eCB/CB1 receptor system contributes to the development of hepatic steatosis remain obscure.

The present study was aimed to delineate whether hepatic PPARα signaling modulates the improved metabolic homeostasis and antisteatotic effects of CB1 receptor blockade. To that end, we tested the efficacy of AM6545, a novel peripherally-restricted CB1 receptor antagonist, in reversing hepatic steatosis and whole body energy metabolism in PPARα$^{-/-}$ mice and their littermate controls.

Chronic treatment with AM6545 was equieffective in reducing body weight and improving glycemic and hormonal control in both mouse strains. However, CB1 receptor blockade by AM6545 reversed the HFD-induced increase in hepatic triglyceride, serum transaminases and liver injury in WT mice, but not in PPARα$^{-/-}$ animals. Additionally, the HFD-induced reductions in hepatic PPARα mRNA expression levels and its target genes were completely reversed by AM6545 treatment in WT controls.

In conclusions, our findings suggest that hepatic PPARα has a significant role in the antisteatotic effect of peripherally-restricted CB1 receptor blockade. Moreover, hepatic steatosis depends on-and therefore can be mitigated by decreased stimulation of hepatic CB1 receptor by eCBs, which will promote PPARα signaling to prevent hepatic steatosis. Such results may support the rationale for the pre-clinical development and clinical testing of peripherally-restricted CB1 receptor antagonists for the treatment of fatty liver disease.

Putative Role of Autophagy in Adipose Tissue Macrophage Lipid Handling

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Background & Objectives: Obesity increases the population of lipid-laden adipose tissue macrophages (ATM foam cells, AT-FC), which were shown to induce insulin resistance in adipose tissue. Autophagy, an evolutionarily-conserved house-keeping process, has recently been implicated in cellular lipid handling, feeding and/or degrading lipid droplets (LD). However, its role in ATM lipid handling is unknown.

Material & Methods: We followed autophagosome and LD dynamics (formation and degradation/disappearance rates) in RAW264.7 macrophages with CYTO-ID (an autophagosome fluorophore) and BODIPY (neutral-lipid dye), respectively, using a live-cell semi-automatic system. For initial LD biogenesis rate, cells were pre-treated with autophagosome formation or degradation inhibitors (3-methyladenine, bafilomycin-A1, chloroquine or leupeptin), followed by lipid loading with 0.2 mM oleic acid (OA) and BODIPY. Complementarily, using a pulse-chase concept, LD degradation was assessed in autophagy-manipulated foam cells.

Results: Effective inhibition of autophagosome degradation required six hours incubation with bafilomycin-A1 and chloroquine (increased autophagosomes area) and two hours for 3-methyladenine (decreased autophagosomes area). The initial rate of LD biogenesis with OA was 4.9±0.57 LD/cell/h. Inhibition of autophagosomes degradation with either bafilomycin-A1, chloroquine or leupeptin increased the initial rate to 7.6±0.76, 7.0±0.77 and 6.2±0.64 LD/cell/h, respectively (Pv

Conclusion: Our results propose a role of autophagy in LD dynamics such, that autophagy inhibition might increase ATM lipid accumulation, thereby supporting FC biogenesis.

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Autophagy-Adipocytokine Cross-Regulation in Adipose Tissue and Adipocytes May Link Obesity to Adipose Tissue Endocrine Dysfunction

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Background/Objectives: Adipose tissue (AT) dysfunction is characterized by altered autophagic activity and pro-inflammatory adipocytokines secretion profile. The objective of this study was to evaluate the bi-directional regulation of obesity-associated changes in adipocytokines profile and dysregulated AT autophagy.

Subjects/Methods: In n=186 human adipose tissue samples we assessed clinical associations between human visceral AT autophagy gene expression and circulating adiponectin, leptin and IL-6, by multivariate models. We used an adipo-cytokine array to assess the effect of autophagy inhibition (with Bafilomycin-A1 or Atg7-siRNA) in mouse adipose tissue and cells. Complementarily, the effect of adipocytokines on autophagy gene expression was assessed in human adipocyte cell line (chub-s7).

Results: Circulating adiponectin, leptin and IL-6 levels were associated with human omental-AT expression of *ATG5 mRNA*, associations that remained significant (beta=-0.330, $p<0.001$; beta=0.344, $p<0.001$; beta= 0.298,$p<0.001$, respectively) in a multivariate model adjusted for age, sex and BMI. Bafilomycin-A1 pre-treatment of AT explants from high fat fed (HFF) mice had no effect on the secretion of some adipose tissue-derived endocrine factors, but partially or fully reversed obesity-related changes in secretion of a sub-set of adipo-cytokines by>35%, including the obesity-associate up-regulation of IL-6, VEGF and TNFα, and the down-regulated secretion of IL-10 and adiponectin. Similarly, siRNA-mediated knockdown of ATG7 increased adiponectin secretion from cultured adipocytes, and partially reversed changes in adiponectin and leptin secretion induced by TNFα+IL-1β. In differentiated human pre-adipocytes progranulin and more robustly - leptin, but not chemerin, increased autophagy gene expression.

Conclusions: Increased AT autophagy is associated with pro-inflammatory adipocytokines profile which alternatively may lead to increased autophagic activity.

Extracts Of Environmental Particles With Low Content Of Organic Compounds Impairs Macrophages' Mitochondrial Respiration And Induce Macrophage-Mediated Adipocyte Dysfunction

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Introduction: Exposure to fine particulate matter air pollution negatively affects human health, but a possible connection with obesity-associated morbidity remains uncertain. Air-pollution-derived compounds may activate immune cells that could then engage in an interaction with adipocytes and contribute to adipose dysfunction. Here we assessed whether immuno-metabolic changes in macrophages exposed to water extracts from diesel exhaust particles (DEP) induce adipocyte dysfunction.

Methods: RAW264.7 macrophages were treated with water extracts of 2 standard DEP with high/low organic compounds content (SRM-1650/2975). Conditioned medium (CM) was collected, and used to expose cultured-adipocytes for 6h. Macrophages' oxygen consumption rate (OCR) was measured by seahorse-XFe-24.

Results: Adipocytes exposed to CM of untreated macrophages exhibited a decreased insulin-stimulated p-Akt/T-Akt and p-Gsk/T-Gsk, and elevated basal lipolysis, compared to control adipocytes. When CM was prepared from macrophages pre-treated with SRM-2975, but not SRM-1650, a further decline in insulin responsiveness was observed. Lipolysis was not further altered. Macrophages' TNFα, IL-10 and IL-6 secretion indicated that these common cytokines were unlikely mediators in this system. This finding suggests involvement of other mediators, or metabolic changes in the immune cells that do not manifest in changes in secretion of common inflammatory cytokines. To this end, already 2h exposure of macrophages to water extracts of SRM-2975, but not SRM-1650, resulted in significant decrease in maximal OCR, without affecting mitochondrial uncoupling. This could not be explained by decreased mitochondrial content, or by expression of mitochondrial respiratory chain proteins, suggesting an acute, functional interference of compounds from SRM-2975 with macrophage mitochondrial respiration.

Conclusion: Results support a potential mediatory role for macrophages in the induction of adipocyte insulin resistance by air pollution particles. Furthermore, it exemplifies that different samples from one type of environmental source may induce different immune-metabolic outcomes that associate with adipocyte dysfunction.

Safety of Thiazide Diuretic Treatment in Patients with Primary Hyperparathyroidism – a Retrospective Analysis

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Introduction: Hypercalciuria is one of the indications for surgery in patients with primary hyperparathyroidism (PHPT). In patients who are ineligible for surgery, medical treatment is limited to controlling severe hypercalcemia and progression of osteoporosis. Thiazides are commonly used to treat idiopathic hypercalciuria, but are usually avoided in PHPT due to possible exacerbation of hypercalcemia. Nevertheless, several reports (up to 13 patients) in the 1990s suggested that thiazide treatment may be safe in patients with PHPT.

Aim: To test the safety of thiazides in patients with PHPT.

Methods: The medical records of patients with PHPT treated with hydrochlorothiazide at a tertiary medical center were retrospectively reviewed. Biochemical parameters, in the presence of 25-hydroxyvitamin D >50nmol/L, were compared for each patient before and after hydrochlorothiazide administration.

Results: The cohort included 72 patients (14 male) of average age 62 years treated with hydrochlorothiazide 12.5-50 mg/day during 3.1±2.3 years. The primary indication for thiazide use was hypertension (n=15) or hypercalciuria (n=57). Treatment led to a significant decrease in mean levels of urine calcium (427±176 to 251±114mg/day, $p<0.001$) and parathyroid hormone (115±57 to 74±36ng/L, $p<0.001$), with no change in serum calcium level (mean: 10.7±0.4 before thiazide, 10.6±1.2mg/dL after, $p=0.4$; maximum: 11±0.5 before thiazide, 11±0.5mg/dL after, $p=0.8$). These findings were consistent over all doses administered, with no difference in the extent of reduction in urine calcium level or change in serum calcium level by thiazide dose.

Conclusion: Thiazides may be both effective and safe for controlling hypercalciuria in PHPT. Efficacy can be achieved even at doses of 12.5mg/day, and safety can be maintained at doses of up to 50mg/day.

The Effect of Glucose Control on Short and Long Term Outcomes Following Surgical Repair of Hip Fracture

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Background: Although data is accumulating on the effect of glucose control during hospitalization for acute illness, the data on the contribution of glucose control during rehabilitation period for short and long term outcomes is limited.

In this study we aimed to examine the effect of glucose control during rehabilitation period after surgical repair of hip fracture on rehabilitation outcomes.

Methods: Diabetic patients after surgical repair of hip fracture have been recruited from rehabilitation center. Glucose control was assessed at the beginning of the rehabilitation period by HbA1c measurement, and during rehabilitation by glucose measurements. The motor and cognitive functional status at admission and at discharge from the rehabilitation was estimated using the Functional Independence Measure (FIM) score. Approximately half of the patients were prospectively followed 3 months after discharge, and functional status was evaluated by telephone conversation. Data on mortality during the rehabilitation and 3 months after discharge was collected.

Results: 64 patients were recruited for the study. The mean age of the patients was 80.73±7.46 years, of whom 78.12% were women and 87.5% were Jews. The median HbA1c at admission was 6.74±0.99%, while mean glucose levels during rehabilitation was 143.72±26.41 mg/dl. No correlation was found between these variables and in-hospital mortality, mortality within the follow-up period, functional status at discharge or functional status at the end of follow-up. The functional status before the hip fracture was associated with better functional status at discharge ($p=0.032$) and showed a trend toward significant correlation with post-fracture mortality ($p=0.058$). Higher FIM scores at the end of the rehabilitation were correlated with lower mortality during the follow up. Maximal glucose level above 250 mg/dl during rehabilitation was associated with increased rate of rehospitalization during the rehabilitation period ($p=0.041$).

Conclusions: Better glycemic control during rehabilitation after surgical repair of hip fracture was associated with decreased rehospitalization rate, but did not influence short and long term functional outcomes or mortality.

Paget`s Disease in Israel - Characteristics of a Large Cohort of Patients Treated at a Single Medical Center

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Introduction: Paget`s disease (PD) is a chronic metabolic bone disease, characterized by focal areas of increased bone turnover. The disease involves one or multiple bones and may cause local and systemic complications. To date, there are no data on PD in Israel.

Objective: To characterize a large cohort of Israeli PD patients treated at a single medical center.

Methods: Medical records of consecutive patients diagnosed with PD who were followed at our medical center between 1992 and 2015 were reviewed for medical, biochemical and imaging data. Patients were included if the diagnosis was confirmed by positive radiography and radionucleotide bone scan.

Results: The cohort included 96 patients (53% male, mean age at diagnosis: 65.1±10.1 years). Only 8 patients were Eighty-three patients (86%) were treated with a bisphosphonate due to active PD (16 etidronate, 49 pamidronate, and 59 zoledronate). Ten and 28 patients who were treated with etidronate and pamidronate, respectively, had disease reactivation and their treatment was switched to zoledronate. Elevated serum total alkaline phosphatase normalized in 38/39 patients (97%) after the first dose of zoledronate. Thirteen patients received additional 1-3 doses of zoledronate, eight of them due to concurrent osteoporosis.

Conclusion: We found several unique characteristics in the present cohort of PD patients compared to previously reported series. These include the absence of clear male predominance, high percentage of monostotic involvement and low percentage of disease complications. We confirm the high efficacy of zoledronate in treating active PD.

Bone Remodeling Markers in Hypertensive Patients With and Without Diabetes Mellitus: Link Between Bone and Glucose Metabolism

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Objective: Growing evidence suggests the presence of a complex interplay between hypertension as well as type 2 diabetes mellitus (DM) and osteoporosis. The present study was designed to investigate a possible impact of type 2 DM on bone remodeling markers such as osteoprotegerin (OPG) and N-terminal propeptide of type 1 collagen (P1NP) in hypertensive patients.

Design and Methods: The 100 study participants were divided into three groups according to presence of DM and hypertension: group one included diabetic hypertensive subjects, group 2 included hypertensive subjects without diabetes and group 3 included subjects without hypertension and DM (controls). Blood sampling for metabolic parameters, including OPG, P1NP, adiponectin, fasting glucose, HbA1C, CRP, HOMA-IR, HOMA-beta function was performed.

Results: Circulating P1NP increased from Group 1 to Group 3 in a continuous fashion. P1NP was significantly lower in hypertensive subjects with DM (Group 1), than in Group 2 and 3 ($p<0.0001$). P1NP, was marginally lower in diabetic hypertensive subjects as compared to nondiabetics with hypertension ($p=0.079$). Circulating OPG did not differ significantly between groups ($p=0.593$).

Conclusions: In the present study, bone formation marker, PINP, was significantly lower in diabetic hypertensive subjects as compared to nondiabetics with and without hypertension. P1NP was inversely associated with parameters of glucose homeostasis such as fasting glucose, HBA1C and positively with HOMA-beta cell function. Type 2 DM was associated with an adverse effect on bone formation independently of age, sex and exposure to antidiabetic drugs.

Increased Risk for Hip Fracture in Winter in the Population of the Negev is Associated with Influenza Infection

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Background: Studies have showed seasonality in incidence of hip fracture with increased risk mainly in winter, the exact pathophysiological explanation for the association is lacking. We hypothesize that seasonal influenza outbreak is a causal link in this association. Therefore we set to examine the association between hip fracture incidence, seasonality, meteorological factors (temperature, amount of rainfall, relative humidity and hours of sunlight) vitamin D levels, and rates of influenza infection.

Methods: This retrospective study included all patients admitted to Soroka University Medical Center with a diagnosis of osteoporotic hip fracture (ICD9 code 820) between the years 2001 and 2013. Patients with malignancies, trauma, and age under 50 were excluded. Demographic data, comorbidities, and vitamin D levels, meteorological data and weekly rates of influenza were collected. Influenza rates were available for the years 2010-2013. In a time series analysis we assessed the association between the daily rate of fractures and the seasonal parameters, using Poisson models. We repeated our model in a subsample of weekly rates of hip fractures to assess the association with influenza.

Results: 4,344 patients with a hip fracture met study criteria (69% females, mean age 78). Daily fracture rates were significantly higher in winter (1.1 fractures/day) compared to other seasons ($p<0.001$). In multivariate analysis adjusted for seasons and spline function of time only low temperatures were associated with hip fractures risk. In subsample analysis, the risk for hip fracture was 1.26 higher two weeks following a week in which the weekly rate of influenza was higher the 95^{th} percentile (CI 1.05;1.51 $p=0.01$), adjusted for seasons and temperature, and temperature ceased to be significantly associated with the fracture risk.

Conclusions: Rates of hip fractures among our population were highest in the winter, and associated with lower temperature, probably due to higher rates of influenza infections which are more prevalent during cold seasons.

Does Adiponectin in Serum or Synovial Fluid Predict Arthroscopy Assessed Cartilage Damage Severity in Patients with Symptomatic Knee Osteoarthritis?

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Objective: Osteoarthritis (OA), the prevalent joint-affecting disease characterized by cartilage damage, is the leading cause of disability in adults and contributes to the excess of morbidity and healthcare costs. We performed the current trial to evaluate biomarkers, specifically adiponectin in serum and synovial fluid, associated with cartilage damage severity assessed by arthroscopy, in patients with symptomatic knee osteoarthritis.

Design: The 40 subjects (mean age 51.8, 35% female, mean BMI 28.8) were divided into two groups according to arthroscopy assessed cartilage damage, using Outerbridge (OB) grading: Group 1 included 20 patients without cartilages surface defects (OB grade 0, I) , Group 2 included 20 patients with cartilages surface defects (OB grade II, III). Metabolic parameters, insulin resistance markers and serum adiponectin levels were determined.

Results: Both groups were similar in terms of serum adiponectin levels ($p<0.806$). Synovial fluid adiponectin levels tended to be lower (not statistically significant) in subjects with cartilage damage (1718.6 vs. 2738.1, $P<0.250$). Knee Society Score was significantly lower in subjects with cartilage damage (113.0+/-24.9 vs. 142.7+/-25.1, $p<0.001$). In multiple linear regression analysis age and BMI were significant independent determinants of cartilage damage in non-obese patients with knee osteoarthritis, such that each 1-unit increase in BMI was associated with a 21.7% increase in risk of cartilage damage (OR1.217, 95% CI 0.998-1.483, $p=0.05$).

Conclusions: We did not find an association between serum adiponectin as well as adiponectin in synovial fluid, and arthroscopy assessed cartilage damage severity. BMI was a significant independent determinant of cartilage damage in non-obese patients with knee osteoarthritis.

An open-label, single center study assessing the efficacy of amorphous calcium carbonate (ACC) supplement in the management of primary hypoparathyroidism.

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Hypoparathyroidism is characterized by the absence or inactivity of parathyroid hormone (PTH), leading to decreased intestinal calcium absorption, reduced bone turnover, hypocalcemia and hyperphosphatemia. Standard treatment in hypoparathyroidism consists of calcium and active vitamin D metabolites. High doses of oral calcium are frequently required.

Study aim: to assess the effect of ACC, a soluble highly bioavailable form of calcium carbonate, on calcemia, calciuria in hypoparathyroid patients(HPP), previously treated with crystalline calcium carbonate supplement (CCS).

Patients and Methods: 10 consecutive HPP, aged 50.9±17.17 years, stable on CCS for at least one year, were enrolled in 28 days study. Patients with renal impairment and conditions influencing calcium absorption were excluded. The total daily dose of elemental calcium supplementation was gradually decreased while replacing CCS by ACC: on day 1, 10% of CCS were replaced by 5% of elemental calcium from ACC; by day 14, 50% of CCS were replaced by 25% ACC; by day 21 100% CCS were replaced by 50%±10% ACC.

Five patients consumed ACC before meals; 5- after meals, the groups were similar in in BMI, age and ethnicity (p=0.17; 0.54; 1.0 respectively). Serum albumin adjusted calcium (SAACa) and serum phosphorus (SP) were evaluated weekly; calciuria - at baseline and at day 28.

Results: Initial elemental CCS doses ranged 1000 -10800 mg/d, alfacalcidol doses ranged 0.25-1.75 mcg/d (remained unchanged during the study period). SAACa and SP were 8.1±0.15 and 4.39±0.186 (mean±SEM) and 8.19±0.14 and 4.4±0.12 (p=0.6;0.9) on day 1 and 28 respectively, while elemental ACC doses ranged 500-5400 mg/d.

During the trial SAACa was maintained between 7.2-9.2mg/dl. One patient had asymptomatic hypocalcemia during physical activity. Two hypercalciuric episodes were observed and treated.

Conclusion: Initial CCS dose was replaced in all subjects with ACC dose of 50% ±10% while SAACa remained stable.

The study was sponsored by Amorphical Ltd., Nes-Tziona, Israel.

Hyponatremia and Decreased Bone Density in Adolescents Inpatients Diagnosed with Anorexia Nervosa

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Objective: Recent studies demonstrated an association between low serum sodium levels and reduced bone density. Patients with anorexia nervosa (AN) are at greater risk for osteoporosis as well as for hyponatremia. The aim of the present study was to assess the association between hyponatermia and bone density in a large cohort of adolescent inpatients with AN.

Methods: A historic cohort study of 174 adolescent females (mean age 15.7±1.8y) hospitalized because of AN between 2003-2013. Demographic and clinical data, including age, psychiatric comorbidity, anthropometric measurements, laboratory tests and bone mineral density (BMD) scores were obtained from the patients` medical charts.

Results: Mean lumbar spine BMD z-score of the patients was lower than average in the normal population (mean -1.5±1.2) and positively correlated with body mass index standard deviation score (BMI-SDS; r=0.42, p0.0001). Sixty-four participants (36.8%) had at least one episode of hyponatremia during the year preceding the BMD measurement. These participants had a significantly lower lumbar spine BMD z-score (-1.8±1.2 vs. -1.3±1.2, p=0.01) compared with participants with no hyponatremia. Lumbar spine BMD z-score was also positively correlated with the levels of free triiodothyronine (r=0.16, p=0.038), 17b-Estradiol (r=0.23, p=0.005) and luteinizing hormone (r=0.25, p=0.001), and negatively correlated with cortisol levels (r=0.33, p0.0001).

Conclusion: Hyponatremia may be associated with decreased bone density in adolescent females with AN. Additional studies are required to evaluate whether the correction of hyponatremia will improve BMD.

Normal Ranges of Basal and Glucagon-Stimulated Free Cortisol in Children

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Background: Standard assays for serum cortisol measurements determine total cortisol (TC) concentrations but not the unbound biologically active serum free cortisol (sFC). Measurement of TC would be greatly influenced by alteration in cortisol-binding globulin (CBG) concentrations. It is, therefore, important to determine sFC levels when CBG levels are either decreased or increased.

Method: Infants and children referred for evaluation of GH and cortisol reserve, underwent glucagon test. Baseline and stimulated serum TC, FC, GH and glucose levels were measured before and every 30 minutes for 180 minutes after IM administration of Glucagon(30 mcg per kg, max of 1 mg). Serum TC and GH were determined by chemiluminescence and serum FC was measured by the same method following equilibrium dialysis. A TC response of 20 mcg/dl was considered normal.

Results: The study group consisted of 62 subjects (26 girls), median age 3.9 years (range, 0.5-13.8). Mean baseline TC and sFC levels were 12.9 ± 6.5 mcg/dl and 0.78 ± 1.1 mcg/dl, respectively. Mean peak TC and sFC levels (150 min) were 29.2 ± 9.5 mcg/dl and 1.7 ± 1.3 mcg/dl respectively. Mean fractions of sFC at baseline and at peak were 4.3 ± 1.6% and 5.2 ± 1.7% reflecting a lower increase in TC (200%) compared to sFC (250%). Peak TC and sFC levels were positively correlated ($r=0.5$ $p<0.001$). The girls had a higher Peak TC and Peak sFC $p=0.004$ and $p=0.03$ respectively. There was a negative correlation between peak TC and age $r=-0.3$, $p=0.02$, however no correlation was found between peak sFC and age $r=-0.06$, $p=0.7$.

Conclusion: Based on these findings, we suggest pilot normal ranges for basal and glucagon-stimulated sFC for children. These norms might serve as a reference when cortisol binding globulin are abnormal. The finding that TC is age dependent while the sFC is not may suggests that the sFC is superior to TC measurement in pediatric population. The higher TC and FC in girls compared to boys might suggest an survival advantage.

Laparoscopic Adrenalectomy for Cushing Syndrome During Pregnancy

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Background: CS in pregnancy is a rare and challenging condition regarding both diagnosis and treatment. We report a case treated surgically in the second trimester.

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

Case Description: A 20 years old healthy woman was admitted at 23rd week of her pregnancy in for evaluation of hypertension known since week 10th of her pregnancy. She presented with striae, acne, hirsutism, facial and truncal obesity. Her oral glucose tolerance test was pathologic with 3 values above the reference. Her basal serum cortisol was 784 nmol/l and her urinary free cortisol 2580 nmol/24hr (N: up to 485). On high dose dexamethasone suppression test urinary cortisol was 2791 nmol/24hr. ACTH level was 12.2 pg/mL (N 5-46). Pituitary MRI revealed a normal pituitary gland. On adrenal MRI a right lipid poor adenoma of 34X26 mm was found. At week 24 of her pregnancy she underwent laparoscopic adrenalectomy due to maternal and fetal risk. The final pathology was consistent with adrenocortical adenoma. Her postop basal blood cortisol dropped to 35 nml/l and steroids replacement was initiated. Cesarian section was performed at week 32 due to fetal bradycardia, delivering a healthy child. At last follow up, 4 months after surgery, she was still on cortisol replacement.

Discussion: The biochemical diagnosis of CS was based on UFC 5x above UNL and lack of suppression on HDDST. Non-suppressed ACTH has been described in CS during pregnancy probably due to placental CRH secretion. The risk of poor outcome was an indication for surgery. Prematurity in this scenario has been reported before, but in our case fetal bradycardia was the reason to induce delivery and probably unrelated to cushing.

Conclusion: The diagnosis of adrenal cushing during pregnancy can be masked by physiological changes in HPA axis. A clinical suspicion should prompt further investigation and treatment be considered in the second trimester.

New Approaches to the Diagnosis and Treatment of Thyroid Disease

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Current approaches to the diagnosis and treatment of hypothyroidism have been in place for many years and include the use of the serum TSH and treatment with L-thyroxine. While effective, new approaches that can determine tissue-specific responses to thyroid hormone would be important in individualized therapy. To accomplish this we are using an *in vivo* approach to identify new biomarkers of thyroid hormone action that will allow us to better interrogate its action across tissues. Finally, to better treat hypothyroidism we have a developed a novel stem cell model that can effectively cure mouse models that lack thyroid tissue. We believe the paradigm developed will allow for development of human thyroid tissue from stem cell progenitors and allow for a new approach for the treatment of hypothyroidism.

Updated Treatments of the Menopause and Beyond

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Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms and other symptoms of the climacteric. Benefits may exceed risks for the majority of symptomatic postmenopausal women who are under age 60 or under 10 years since the onset of menopause. MHT should be recommended for women with moderate-to-severe vasomotor symptoms, in the absence of contraindications. Such criteria apply to approximately 20% of women in early menopause. Health care professionals should individualize therapy based on clinical factors and patient preference. They should screen women before initiating MHT for cardiovascular and breast cancer risk, and recommend the most appropriate therapy depending on risk/benefit considerations.

Current evidence does not justify the use of MHT to prevent coronary heart disease, breast cancer, or dementia. Other options are available for those with vasomotor symptoms who prefer not to use MHT or who have contraindications.

Low-dose vaginal estrogen provides effective therapy for the genitourinary syndrome of menopause, and vaginal moisturizers and lubricants are available for those not choosing hormonal therapy.

All postmenopausal women should embrace appropriate lifestyle measures, such as exercise.

Future technologies aiming to proliferate stem oogonial cells may prolong the reproductive period and delay menopause, thus may prove to be the ultimate prevention of the climacteric syndrome.

Menopausal Hormone Therapy for Breast Cancer Survivors

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ההסכמה הרווחת היום היא שאין לתת טיפול הורמונלי לנשים שהחלימו מסרטן השד וסובלות מתסמינים קלימקטריים.

הבעיה, שגם נשים שהחלימו מסרטן השד מבקשות עזרה בשל סבל קשה מגלי חום, הזעות, הפרעות בשינה, דכאון ותסמינים אחרים של גיל הבלות שפוגעים קשה באיכות חייהן. כמובן שקו הטיפול הראשון שיוצע יכלול טיפולים אלטרנטיביים וקו שני יכלול תרופות דוגמת קלונדין, פרוזק, גבאפנטין ועוד, שמשפיעים לעתים על חלק מתסמיני גיל המעבר. מיעוט קטן של נשים שהחלימו מסרטן השד, שאיכות חייהן כה ירודה, יסכימו לקבל אפילו טיפול אסטרוגני ובלבד שהתסמינים הקלימקטריים יוקלו. ההחלטה באם לתת לנשים אלו טיפול הורמונלי ובאיזה שילוב טיפולי, תוכפף לקווים מנחים שמטרתם לצמצם ככל שניתן את האפשרות להישנות סרטן השד במטופלת.

הקווים המנחים כוללים:

שימוש מינימלי או הימנעות מפרוגסטרון בנוסף לאסטרוגן.

נקיטת גישה מקלה לנשים להן נמצאו בלוטות לימפה שליליות.

שילוב SERM כגון טמוקסיפן (או מעכבי ארומטז)ובעתיד גם מעכבי סולפטאז (עם הטיפול האסטרוגני.

נקיטת גישה מקלה לנשים להן סרטן השד היה שלילי לרצפטורים לאסטרוגן.

שימוש בקווים מנחים אלו בטיפול בנשים שהחלימו מסרטן השד, שהטיפול האסטרוגני היה המוצא האחרון שאפשר להם חיים סבירים, עשוי לצמצם במעט את הסיכון להישנות סרטן השד אצלן.

Impact of Yesterday's Genes and Today's (Diet and) Chemicals on Tomorrow's Women

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There are over 100,000 chemical compounds in industrial use, with another 2000 added annually. We have become more aware of the impact of many of these chemicals on the human body, particularly those that interfere with hormones and the adipocyte, termed "endocrine disrupting chemicals" and "obesogens". This presentation will explore the concepts of "windows of susceptibility" (times during development that are critical to environmental exposures), contemporary puberty in girls, and results of recent studies examining the impact of proposed endocrine disrupting chemicals on timing of pubertal events.

Endocrine Disrupting Chemicals (EDCs) and Male Reproduction

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Male reproduction is not only essential for human survival, but also an important marker of general health. Furthermore, male reproduction, which is controlled by hormones both during fetal development and adulthood, is sensitive to environmental impacts. Consequently, male reproduction is a good model to advance scientific understanding of environmental impact on health, and specifically, the impact of endocrine disrupting chemicals (EDCs). Recent reports on declining semen quality and increasing rates of cryptorchidism, hypospadias and testicular germ cell tumors as well as androgen insufficiency in adulthood led to the hypothesis that these conditions may co-occur and contribute to a syndrome, termed the Testicular Dysgenesis Syndrome (TDS). According to this hypothesis, these conditions may arise from a common origin, testicular dysfunction during prenatal development, which may, at least in part, be linked to developmental exposure to EDCs.

I will present recent evidence supporting an adverse impact of EDCs on male reproduction, including on the anogenital distance (AGD), a marker of the fetal hormonal milieu, and will discuss future directions of this research as well as its implications for health policy.

Neutrophils in Cancer, Old Controversies and New Perspectives

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Traditionally, cancer research focused on studying cancer cells towards identifying weaknesses that may be exploited therapeutically. However, in recent years the critical roles played by the non-malignant cells that make the tumor stroma became apparent. The tumor stroma consists of immune cells, endothelial cells, fibroblasts etc. which were found the promote tumor growth and progression. In this context, the role played by neutrophils remains a matter of debate. Neutrophils are the most abundant of all white blood cells in the human circulation and are usually associated with fighting infections and with inflammation. In cancer, neutrophils were shown to provide a variety of pro-tumor functions including secretion of tumor promoting cytokines, degradation of the ECM and immune suppression. In contrast, neutrophils were also shown to have the capacity to kill disseminated tumor cells either through direct or antibody-dependent cytotoxicity. These conflicting reports suggest that although neutrophils are largely viewed as a homogeneous population they may consist of distinct subsets with significantly different properties. Indeed, previous studies have shown that neutrophil function may be dramatically affected by environmental cues in the tumor microenvironment. Furthermore, our recent data suggest that circulating neutrophils in cancer are heterogeneous consist of both low (LDN) and high-density (HDN) subsets. HDN present with a mature morphology and maintain a pro-inflammatory, anti-tumor phenotype. In contrast, LDN that appear transiently in self-resolving inflammation, accumulate continuously with cancer progression and present with a mixed morphology, a reduced inflammatory profile, impaired functionality and immunosuppressive properties. In early tumor development HDN are the predominant neutrophil subpopulation giving neutrophils, in general, an anti-tumor phenotype. However, with tumor progression, LDN are preferentially propagated to the extent that they become the dominant circulating neutrophil subpopulation. When this happens the overall neutrophil contribution switches from anti- to pro-tumor. Our observations identify dynamic changes in neutrophil subpopulations and provide a mechanistic explanation to mitigate the controversy surrounding neutrophil function in cancer.

Fracture Liaison Service in the Negev- 18 Months of Fracture Prevention

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Background: Osteoporotic hip fractures are a growing medical and financial burden. Patients with a prior osteoporotic fracture are at increased risk for recurrent fractures. Only 20% of patients with a hip fracture receive anti-osteoporotic treatment following hospital discharge. A multidisciplinary fracture liaison service (FLS) has been shown to increase treatment rates, decrease recurrent fractures by 25% and to be cost effective. It was therefore our aim to create a FLS at Soroka University Medical Center (SUMC).

Methods: A FLS including a nurse and a coordinator supervised by the Endocrinology department has been created in July 2014. All adults over age 50 admitted to the orthopedic department at SUMC with a hip fracture are offered to join the project. The FLS nurse collects data regarding past medical history and medications, detailed history for osteoporosis and its risk factors, functional level, risk of falls, calcium and vitamin D intake. Patients undergo basic lab work and are given a loading dose of vitamin D. At the first outpatient orthopedic visit patients are consulted by an endocrinologist that assigns an anti-osteoporotic medication that is most appropriate according to their medical condition and current guidelines for the treatment of osteoporosis.

Results: As of December 2015, 497 patients were admitted with hip fracture to SUMC, of whom 309 joined the project; mean age 79.59, 74% females. 34.7% had a previous osteoporotic fracture but only 13.3% received medical treatment for osteoporosis prior to fracture. Preliminary results available for the first 167 patients show that following our intervention 80% of patients received medical treatment for osteoporosis as following: 14% oral bisphosphonates, 40%. Zoledronic acid, 24% Denusomab and 4.8% Teriparatide. During the study period 2 patient encountered a recurrent hip fracture.

Conclusions: FLS has been implemented at SUMC with promising results after 18 months. Reduction in recurrent fracture rates requires long term follow-up. In-hospital treatment is examined as a mean to increase anti osteoporotic treatment rates.

Familial Hyperparathyroidism: Results of Genetic Screening for Familial Hypocalciuric Hypercalcemia Type 1 and 3

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Background: Primary hyperparathyroidism is due to parathyroid adenoma in most of cases. Familial clustering of hyperparathyroidism suggests involvement of a genetic background.

Objective: to report results of initial genetic screening performed in cases of familial primary hyperparathyroidism.

Methods: familial hyperparathyroid cases without identification of parathyroid adenoma on imaging work-up or after failed surgery were recruited at the endocrinology and metabolism service at our institution, or addressed for further evaluation by expert endocrinologists in Israel. After informed consent was signed, blood for DNA extraction was obtained and genetic sequencing for the gene encoding the Calcium-Sensing Receptor (*CaSR*) was performed. In negative cases, we further performed sequencing of the *AP2S1* gene encoding the Adaptor related Protein complex 2.

Results: 7 index cases with at least one first-degree relative presenting features of primary hyperparathyroidism without identified adenoma after neck ultrasound and MIBI-scintigraphy or after failed surgery, were recruited. Among them 4 had a low fraction excretion of calcium less than 1%, a typical feature of familial hypocalciuric hypercalcemia (FHH), whereas 3 other did not. Screening of the *CASR* gene yielded one patient with a novel heterozygous mutation, c.554G>A (p.I32V). We identified 2 additional patients carrying the deleterious recurrent mutation c.44G>T (p.R15L) in the *AP2S1* gene.

Conclusion: Screening for mutations in *CaSR* and *AP2S1* is worthwhile in patients with familial hyperparathyroidism and typical features of FHH. However, some cases may not present with the typical low fraction excretion of calcium. In negative cases, it remains to evaluate FHH type 2 with mutations in the GNA11 gene (G-protein Subunit α_{11}) and other potentially involved genes.

Bone Mineral Density in Prader Willi Syndrome: A Search for Genetic Markers

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Prader-Willi syndrome (PWS) is characterized by variable and heterogeneous expression of physical, cognitive, endocrine, and behavioral disorders associated with the lack of paternally expressed imprinted genes at 15q11.2-q13. Diminished bone mineral density (BMD) and osteoporosis are frequent in PWS. No associations have been found between BMD and any of the genes in the PWS region. The purpose of our study was to investigate polymorphisms of candidate genes shown previously to be correlated with osteoporosis and/or bone disease with BMD in PWS patients.

Blood samples were collected from 96 individuals (46 males; 50 females) aged 3.5-47.9 years (mean±SD 16.6±9.7y) with PWS. DNA samples were tested for 12 polymorphisms in 8 candidate genes [Interleukin-1 (IL1-alfa, IL1-beta, and IL1RN), CYP1A1, Low Density Lipoprotein Receptor-Related Protein 5 (LRP5), vitamin D receptor (VDR), RANK and RANKL]. All patients underwent BMD measurements using a Hologic Dual Energy x-ray absorptiometry (DXA) machine at the femoral neck and lumbar spine. Abnormal BMD was defined as Z-score

Sixty-seven subjects (70%) had abnormal BMD (the youngest was 3.7 years old), 25 (26%) had osteoporosis (the youngest was 6.8 years old). BMD negatively correlated with age ($p<0.001$) and BMI ($p=0.006$), but did not correlate with sex, estradiol, or testosterone levels. BMD correlated significantly with genotype IL1 alpha C889T ($p=0.031$), genotype Cyp1A1 C4887A ($p=0.04$) and VDR FOK I genotypes (ff /Ff/FF) ($p=0.002$); FF genotype has a protective effect. After correcting for age, correlations were significant only for VDR.

In summary, individuals with PWS have low BMD/osteoporosis at a much younger age than the general population. The significant correlation between VDR genotypes and BMD is not specific for PWS. Other genetic and non-genetic factors increase the risk of osteoporosis in PWS. Treatment with vitamin D, calcium, and hormone replacement should be considered in this population.

The Role of Hepatic Intra-arterial Therapies in Metastatic Neuroendocrine Tumours (NETs): A Specialist Center Experience

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Background: Liver metastases are relatively common in patients with neuroendocrine tumors (NETs), having a negative impact on disease prognosis. The options for selective liver metastases therapy in patients with advanced unresectable NETs are limited to catheter guided procedures: TACE (transarterial chemoembolization), TAE (transarterial embolization) or SIRT (selective internal radiation therapy). However, data regarding the effectiveness and safety of these procedures in different types of NETs is limited.

Aim: To explore the clinical outcome, survival and safety profile of catheter-guided therapies for liver metastases in a group of NETs patients of different origin.

Methods: Retrospective case series of consecutive patients (mean age 60.9 years, 57% female) treated at a single tertiary university medical centre from 2005 to 2015. Medical records were reviewed for demographic data, laboratory and clinical course, treatment, tumor response and long-term outcome.

Results: 45 consecutive patients with G1, G2 and low G3 NETs of different origins with liver metastases were retrospectively investigated (UKO, 7; gastric carcinoid, 2; small bowel, 11; rectal, 3; PNET, 12; lung, 3 and MTC, 7). 43 patients underwent TACE, and 2 patients underwent SIRT. Clinical improvement as well as tumor response (SD+PR) was observed in 43/45 patients (96%). The median time to tumor progression following the first treatment was 12.3 ± 1.2 months. The median overall survival for the entire group was 23.33 ± 6.5 months, and it was more pronounced in the MTC subgroup, whereas for the small bowel, for PNET and UKO subgroups results were similar. There was a trend for a better survival time in patients without extrahepatic metastasis than in patients with extrahepatic disease. Noteworthy, primary tumor resection had a beneficial effect on the survival.

Conclusion: Hepatic intra-arterial therapies are well tolerated and associated with both clinical improvement and tumor stabilization for prolonged periods of time in the majority of patients with NETs and liver metastases of varying origin. These therapies should be always considered, irrespective of the presence of extrahepatic metastasis.

Novel Genetic Changes in Autosomal Dominant, ACTH Independent Macronodular Adrenal Hyperplasia Associated with Hypercortisolism and Giant Adrenals

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ACTH independent macronodular adrenal hyperplasia (AIMAH) is a rare cause of Cushing's syndrome. Both Phosphodiesterase 11A4 (PDE11A4) mutations and inactivating mutations of armadillo repeat containing 5(ARMC5) have been associated with familial AIMAH. A family with autosomal dominant AIMAH was studied trying to elucidate the involved genetic basis.

Methods and Results: Adrenal hypercortisolism with giant bilateral AH was diagnosed in three adult members of the family, a mother and two sons. Further evaluation excluded the presence of aberrant receptors. Bilateral adrenalectomy of the index case was performed showing huge adrenal glands (460 gr). DNA were extracted from peripheral blood lymphocytes. Sequencing of ARMC5 coding region in the proband revealed a novel heterozygote mutation, S767X. Interestingly, sequencing of PDE11A4 coding region revealed a heterozygote rare variant R867G, that has frequency of 2-3% in the general population. PDE11A4 gene defects have been associated with Carney complex and AIMAH, including R867G, probably acting as a phenotype modifier. Inmunohistochemical studies of the excised adrenal tissue showed a very low expression of PDE11A4 and ARMC5 compared to normal adrenals. The family was screened for hypercortisolism, adrenal hyperplasia (MRI) and genetic testing. All the patients with AIMAH carried both variants. Other siblings carrying either one mutation or none were healthy, with normal adrenal size. A 15 years old daughter of the index case harbored both variants, but her HPA axis evaluation was normal and the adrenals showed a normal size.

Conclusions: A family with ADAIMAH causing giant adrenal hyperplasia associated with a novel mutation in ARMC5 in conjunction with PDE11A4 mutation, causing low protein expression is reported. Coexistence of PDE11A4 variant in all three affected individuals may indicate a phenotype modifier role. Because clinical and biochemical abnormalities appear during adulthood, young phenotypically normal mutation carriers may be at risk of developing clinical disease in the future.

Cushing`s Syndrome in Israel - New Incidence Data

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Introduction: Endogenous Cushing`s syndrome (CS) is rare, with a reported incidence of 0.7-2.4/ million/year. Surprisingly, this rate is based on only two population-based studies from 2001 and 1994.

Objectives: To investigate the incidence of CS in the last decade and the performance of urinary cortisol screening.

Methods: The study was conducted at Maccabi Healthcare Services. All 24-hour urinary free cortisol (UFC) tests registered in the computerized database from 2005 to 2014 were analyzed. Patients with results 3 times above normal range (UFCX3) were identified, and their medical files were reviewed for a subsequent diagnosis of CS by an expert endocrinologist. Findings were evaluated for patterns in CS diagnosis and UFC testing over time.

Results: Of 43,685 patients who underwent UFC tests, 226 (0.5%) had UFCX3. Eighty-five (37.6%) were diagnosed with CS, 77 of them during the study years (58 female, mean age 46.1±14.1 years). Of 74/77 patients with consistent data, 43 had Cushing`s disease, 26 adrenal Cushing, and 5 ectopic ACTH secretion. The annual incidence of CS was 4.1±1.2 new cases/million/year (median 4), with no significant change between 2005 (4.7/million) and 2014 (5.4/million). The number of UFC tests increased steadily, from 1850 in 2005 to 6467 in 2014. However, there was no clear trend of an increase in the absolute annual number of UFCX3 results (mean: 22.6±9.1/year). The most common reason for UFC measurement was obesity. Of 44 patients with UFCX3 tested before bariatric surgery, only 1 was diagnosed with CS. The most common reason for false-positive UFC results was exogenous steroid use (62/141 patients)

Conclusions: The incidence of CS is higher than previously suggested. Although the number of UFC tests performed is dramatically increasing, the number of UFCX3 results and the incidence of CS remain quite stable. The expected yield of routine UFC before bariatric surgery is low.

Five-Hour Serum Cortisol Concentration Profile after Hydrocortisone Loading – an Effective Tool for Optimization of Replacement Therapy in Adrenal Insufficiency

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Background: Titration of glucocorticoid replacement therapy in adrenal insufficiency is mostly based on clinical assessment, due to the lack of precise laboratory tools for treatment monitoring. Overdosing might lead to increased morbidity including hypertension, weight gain, diabetes and osteoporosis whereas underdosing may result in life threatening adrenal crises. We examined the efficacy of hydrocortisone curves as an objective tool for dose titration.

Methods: Retrospective review of hydrocortisone loading curves performed in adrenal insufficient patients between 2008 and 2015 in our institute. Serum cortisol levels were measured prior and 30, 60, 120, 180, 240 and 300 minutes following administration of the patient`s regular morning hydrocortisone dose. Dose adjustments were performed by the treating physician based on cortisol profile results. Metabolic data, including weight, blood pressure and lipid profile were documented before and after performance of the curve.

Results: Sixty five hydrocortisone loading curves were performed in 51 patients during the study period. Pertinent clinical data was available for 28 patients. Mean age 44.8±13.7 years, 43% males, average weight was 82.9±21.9kg, 36% were hypertensive and 25% had diabetes. Mean daily hydrocortisone dose was 23.1±7.3mg. Based on cortisol curve results, the dose was decreased in 54% of patients, unchanged in 36% and increased in 11%. There were no statistically significant between-group differences in age, sex, starting dose, starting weight, diabetes and hypertension prevalence. The average dose change was -8.2mg in the dose reduction group and +1.5mg in the rest of the study population ($p<0.05$). The average change in blood pressure was -11.38/-9.13 in the dose reduction group as compared to +0.8/+2.9 in the rest of the study population ($p<0.05$). A statistically non-significant reduction in weight, LDL and total cholesterol levels was also noted in the dose reduction group.

Discussion: Our findings suggest that cortisol curves are an effective tool for hydrocortisone dose titration, leading to a significant reduction in blood pressure in this cohort

A Founder CISD2 Mutation (Wolfram Type 2) is a Common Cause of Anti-GAD Negative "Type 1 Diabetes"

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Background: Wolfram syndrome is a genetic disease, known to cause pediatric diabetes, neurodegeneration with optic atrophy and hearing loss. Recently, a similar phenotype -Wolfram syndrome type 2 (WFS2) - associated with childhood GI ulcers and bleeding was identified as caused by CISD2 gene mutation. Only 4 families and 2 mutations were so far reported.

Methods and Results: We report patients from 6 different Palestinian families who presented as type 1diabetes and treated by insulin that also had a history of a wide variety of gastrointestinal (GI) symptoms associated with pediatric upper GI bleeding/ulcer. Following the finding of negative anti GAD antibodies and further investigation into mild (ignored) visual/acoustic symptoms we sequenced the CISD2 gene. In all 6 families the homozygous IVS1+6G>C, p.E37Q mutation was identified, causing skipping of the 2nd out of 3 exons of the CISD2 gene. Studying 8 microsatellite markers flanking the CISD2 gene indicated a founder effect in all 6 unrelated families. Furthermore, restriction enzyme analysis of 200 healthy control alleles (same ethnic background) showed a surprising high carrier rate of 1/40-2.5%. The presence of c-peptide in the index case serum and the current understanding of CISD2 function in preventing oxidative stress and beta cell apoptosis lead us to try using oral hypoglycemics for this WFS2-diabetes. Given the known protective effect of GLP-1 against ER stress-mediated cell death, using the combination of Metformin and Sitagliptin (Januet) enabled successful weaning from insulinwhile achieving a good glycemic control (HbA1c – 7.2%) in our first patient.

Conclusion: Early manifestation of GI symptoms in anti-GAD negative "type 1 diabetes" should lead to suspect the relatively common diagnosis of WFS2 caused by a founder CISD2 mutation. Insulin may be switched to incretin based oral therapy. Further mechanistic studies are required to establish the most effective oral hypoglycemic therapy for WFS2.

Resistin/Adiponectin/FGF21 Interplay in SH-SY5Y Neural Cells and DIO Rodents: a Novel Mechanism Contributing to Insulin Resistance

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Obesity and type2 diabetes share several features such as insulin resistance and energy homeostasis deregulation driven by changes of adipose tissue secreted hormones. Two such adipokines: adiponectin, an insulin-sensitizing hormone, and resistin known to promote insulin resistance are thus potential links between obesity and type2 diabetes. In addition, Fibroblast growth factor 21 (FGF21), predominantly produced by the liver, has similar effects as adiponectin in regulating glucose and lipid metabolism and insulin sensitivity. In the present study, we investigated whether central resistin promotes insulin resistance through the impairment of adiponectin signalling and by promoting FGF21 resistance. Chronic ICV resistin infusion to rats down-regulated both hypothalamic and hepatic APPL1, a key protein in adiponectin signalling, associated with decreased Akt/APPL1 interaction and an increased Akt association with its endogenous inhibitor TRB3. Resistin treatment also reduced the expression of adiponectin receptors in hypothalamus, liver, muscle and adipose tissue. Furthermore central resistin acting through TLR4 impaired insulin sensitivity consequently to the downregulation of FGF21 and its receptor components in the hypothalamus and peripheral tissues promoting FGF21 resistance. We also showed that resistin effects are abolished in TLR4 knock-out mice and in SH-SY5y human neural cells expressing TLR4 siRNAs. In summary, our study reveals novel mechanism explaining the link between insulin resistance and central resistin/TLR4 pathway that impairs adiponectin signaling and in parallel promotes FGF21 resistance. Blocking resistin signaling by resistin antagonist developed by our groups may thus serve as a novel tool for clinical intervention.

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The Effect of Glucose Control During Hospitalization in Internal Medicine Wards on Morbidity and Mortality Among Elderly Patients

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Background: The glycemic target for non-critically ill hospitalized patients has not been determined yet. Guidelines recommend premeal glucose levels

The aim of this research was to define an association between blood glucose levels and the method of glucose control on morbidity and mortality in elderly patients during hospitalization in internal medicine wards.

Methods: Hospitalizations of elderly subjects 65 years and older diagnosed with diabetes mellitus (DM) were recorded. Patients who died or were discharged less than 72 hours from hospitalization were excluded. Epidemiological and clinical data were extracted from the electronic files.

Results: Data on 566 hospitalizations of elderly patients with known DM were retrieved. Mean patient age was 79.5± 7.9 years, of whom 51.6% were males and 82.2% were Jews. .Participants were stratified into four groups according to mean glucose level during hospitalization (≤140 mg/dl, 141-180 mg/dl, 181-220 mg/dl, and ≥ 221 mg/dl). Mean glucose level 180 mg/dl during the hospitalization was associated with higher mortality rates (p=0.001) and longer hospitalization (p=0.014) but not with higher risk for hypoglycemia (p=0.736) or mechanical ventilation (p=0.48). The difference in mortality rates remained statistically significant after a multivariate analysis adjusted for age, body mass index, hospitalization length and hypoglycemia. The method of glucose control (insulin, oral hypoglycemic agents, combination or no treatment) did not affect mortality rates, although the use of insulin alone or in combination with oral hypoglycemic drugs was associated with significantly more hypoglycemia events.

Conclusions: In this cohort, mean glucose level of 180 mg/dl in non-critically ill elderly diabetic patients was associated with significantly lower mortality rate and shorter hospitalization duration with no excess of hypoglycemia risk.

Mortality of Admitted Patients with Diabetes Mellitus According to Treatment (MADMAT Study)

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Aims: To investigate the importance of treating diabetes mellitus by evaluating morality rates of untreated and medically treated diabetic patients admitted to a tertiary care hospital.

Methods: Historical prospectively collected observational data derived from the electronic records of hospitalized patient ≥18 years, admitted for any-cause to medical wards, between January 2011 and December 2013. Data were analyzed for comorbidities and mortality in relation to the absence/presence and nontreatment/treatment of diabetes. Main outcomes were all-cause mortality at various time points.

Results: The cohort included 35,340 patients, 51% male, of median age 70 years at admission; 24,159 without diabetes and 11,181 with diabetes. Within the diabetic group, 2,188 patients (20%) were not receiving medical treatment for diabetes and 8993 were being treated as follows: 4550 (41%) non-insulin monotherapy; 1550 (14%) non-insulin combination therapy; and 2,893 (26%) insulin. The patients with medically untreated diabetes had higher in-hospital, 30-day, and 12-, 24- and 36-month mortality rates than the treated diabetic patients. Overall mortality rate during follow-up was 31% for the whole cohort and 28% for the nondiabetic patients. Rates in the diabetic patients by treatment were as follows: 46%, no medical treatment; 34%, monotherapy; 25%, combination therapy, and 45%, insulin. Rates of hypertension, ischemic heart disease, chronic renal failure, and congestive heart disease were higher in the untreated and insulin-treated diabetic patients than in the nondiabetic patients and the diabetic patients on non-insulin treatment.

Conclusions: Lack of treatment for diabetes mellitus might have serious consequences. A targeted treatment approach may decrease complications and mortality.

Early Insulin Secretion Defect and Matenal Inheritance Characterizes Males with Type 2 Diabetes of Yemenite Origin

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Aims/Hypothesis The aim of the current study was to characterize β-cell function, insulin sensitivity and line of inheritance in patients with recent-onset Type 2 diabetes of Yemenite (Y-DM) and non-Yemenite (NY-DM) Jewish origin. We hypothesized that the dramatic increase in the prevalence of diabetes observed in Yemenites who immigrated to Israel may be related to reduced β-cell ability to cope with Westernization and weight gain.

Methods: A 180-minutes meal tolerance test (MMT) was performed in 121 GAD negative patients, 59 Y-DM, 62 NY-DM, treated by diet ± oral antihyperglycemic monotherapy. Based on MMT, indexes of insulin resistance and secretion were calculated.

Results: There were no significant differences in age, sex, diabetes duration, BMI, HbA1c and lipid profile. A significant difference was found in family history: 63% of Y-DM had maternal inheritance vs. 35% in NY-DM ($p<0.001$). Both indexes of β-cell function, the insulinogenic and the disposition indexes were significantly lower in Y-DM compared with NY-DM (0.66±0.4 vs. 0.93±0.8, $p=0.04$; 2.3±1.8 vs. 3.3±3.3, $p=0.04$, respectively) with no difference in insulin sensitivity.

When females and males were analyzed separately, the difference in maternal inheritance remained significant in both but the difference in β-cell function indexes was observed only in males ($p=0.03$, $p=0.01$, respectively).

Conclusions/Interpretation: Y-DM males have a significant reduction of β-cell function and reduced ability to compensate for insulin resistance compared with NY-DM males. Both males and females of Yemenite origin have a significantly higher maternal inheritance. These data suggest different underlying mechanisms leading to early loss of β-cell in Y-DM.

The Myth Behind the Normo-Metabolic Obesity: the Correlation Between Metabolic Syndrome Components and Weight Starts at the Low-Normal Weight and Extends Continuously All the Way to Obesity

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The entity "Normometabolic-obesity" has received much attention, but most analyses allowed the inclusion of 1-2 components of the metabolic syndrome (MS). Hence the so called normometabolic obese is not entirely normal. We analyzed 9329 subjects at Tel-Aviv medical center. 6795 examinees had no criteria of the MS (MS score=0) with BMI ranging 19-39 kg/m^2. At a BMI=19, 20% of the cohort had at least one component of the MS, thereby rising linearly with BMI, such that at BMI=29kg/m^2, 83% of the examinees already had MS $\geq$1. As related to BMI at this range, the distribution of subjects with 1, 2, 3, 4 or 5 components of the MS (score 1-5) was Gaussian, and shifted to the right with the increase in the number of MS components. To scrutinize this phenomenon, we examined the relation to BMI of 5 MS-related measures: BP, HDL, triglycerides and liver-enzymes in MS=0 subjects. For the 6502 subjects whose BMI ranged between 19-29 Kg/, there was a linear increase of systolic BP (from 106-116 mmHg), diastolic BP (69-75 mmHg), glucose (55-100mg%) triglyceride (69-90 mg%), SGOT (21-24 U/L), SGPT (10-27 IU/L) and a decline in HDL (70-55mg%). When 3838 BMI$\geq$ 30kg/m^2 subjects were analyzed, a normometabolic state (MS score 0-1) was BMI-related, and decreased to 7% by BMI=37kg/m^2. Still, ***adjusted for BMI***, there is significant clustering of high levels (upper quartiles) of blood pressure, triglycerides, glucose and CRP, liver enzymes and low HDLc. Finally, women are metabolically protected relative to men of the same BMI/waist circumference/age.

Conclusion: A) MS components rise linearly with BMI B) The normometabolic state is uncommon in obese subjects, and its rate declines steeply with increasing BMI and age. C) Higher systolic BP levels co-cluster with increased levels of glucose/triglycerides/CRP/LDL/GOT/GPT and lower HDL. D) Women are more metabolically protected in comparison to men.

T-Cell Receptor Repertoires in Type-1 Diabetes are Promising Biological Markers Linking Genetics and Disease

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Type 1 Diabetes (T1D) results from failure of self-tolerance that relies on deletion or suppression of T-lymphocytes whose T-cell receptors (TCR) recognize autoantigens specific for the pancreatic β-cells. The TCR's ability to recognize antigens depends on somatic recombinations of the genes for α and β chains of the TCR in each lymphocyte. This involves numerous combinations from a large number of V (variable), J (joining) and D (diversity) for the α and β chains. TCRs recognize antigens only if presented by the polymorphic HLA molecules. As TCRs interact with both HLA and antigen in the thymus, it is to be expected that the HLA genotype bias's the choice of V, J and D segments. We suggest that T1D susceptibility conferred by high-risk HLA haplotypes involves favoring a finite set of V, J and D segments in the rearranged TCR.

Pioneering this approach we recruited from our clinic 35 patients and 7 controls from which RNA was extracted from peripheral-blood naïve CD4+ T-cells. A 5'-rapid amplification of cDNA ends (RACE) protocol that we have developed allowed the unbiased amplification of all TCRs. Amplicons were sequenced using the *Illumina* MiSeq and V, J and D segment choice assigned by the IMGT algorithm. HLA genotypes were defined for all study subjects of the study.

We found specific changes in TCR repertoires that associate with T1D HLA risk alleles; show that such changes can be used to classify T1D patients from controls; and identify in the naïve TCR repertoire of T1D patients higher numbers of TCRs that are associated with known islet antigens. Our results shed a new light on mechanisms contributing to T1D pathogenies, link genotype and disease, and provide useful new biomarkers for prediction, prognosis and treatment.

Cancer Protection in Laron Syndrome Patients is Associated with IGF-1 Dependent Increase in Thioredoxin Interacting Protein (TXNIP) Gene Expression

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Background: Laron syndrome (LS) is a congenital autosomal recessive disorder caused by molecular defects (deletion or mutation) of the growth hormone (GH) receptor (GHR) gene. These defects lead to GH insensitivity and, consequently, congenital IGF1 deficiency. The IGF system has a key role in mediating growth, differentiation and developmental processes. Overexpression of IGF1 or its receptor (IGF1R) is a typical hallmark of most tumors. Consistent with the prosurvival, antiapoptotic role of IGF1, recent epidemiological studies reported that patients with congenital IGF1 deficiency have a reduced risk of cancer development and, potentially, resistance against oxidative stress. The thioredoxin interacting protein (TXNIP) plays an important role in redox homeostasis, glucose metabolism and cellular homeostasis. In addition, TXNIP has been identified as a candidate tumor suppressor gene in various types of cancer. The aim of our study was to investigate the involvement of the TXNIP gene product in IGF1R signaling pathways associated with protection of LS patients from cancer. In addition, we explored the involvement of TXNIP in the oxidative stress response.

Methods: HEK293 and prostate cancer-derived cell lines P69 and M12 were used in this study. Quantitative Real time PCR (qRT-PCR) was carried out following hormonal treatment at different time points. Expression levels of receptors, proteins and activation of signaling cascades were measured by Western immunoblotting.

Results: Genomic analyses conducted on lymphoblastoid cell lines derived from LS patients and healthy controls of the same age, gender and ethnic group revealed that TXNIP mRNA levels in LS patients were several-fold higer than in controls. Genomic data was validated by qRT-PCR. In addition, qRT-PCR revealed that IGF1 and insulin significantly downregulated TXNIP gene expression in a time-dependent manner, in both normal and prostate cancer cell lines. Furthermore, Western blot analysis revealed that oxidative stress (Hydrogen peroxide treatment) significantly increased TXNIP expression.

Conclusions: Our preliminary analyses have identified an important novel link between the TXNIP gene and the IGF1R signaling pathway, with potential implications in cell homeostasis during oxidative stress. Further studies will be carried out to dissect the TXNIP-mediated mechanisms at the molecular and cellular levels. Our studies are expected to generate novel information of both basic and translational nature regarding cancer protection pathways in LS patients.

Luminal STAT5 Mediates H2AX Promoter Activity in Distinct Population of Basal Mammary Epithelial Cells

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Deregulated STAT5 activity in the mammary gland caused latent, parity dependent, tumorigenesis with pregnancy being the vulnerable period. Under pregnancy-like condition, epithelial cell cultures with hyper STAT5 activity expressed higher levels of H2AX compared to their intact ones. Higher H2AX expression may cause tumorigenesis. Here, we aimed at linking high STAT5 activity to reporter H2AX-GFP expression, looking for distinct types of mammary cell populations that express these proteins. Both in vitro and in transgenic mice only 0.2-0.02% of the cells expressed the H2AX-GFP hybrid gene, respectively. Its expression in enriched populations correlated with that of the endogenous H2AX gene, suggesting that detectable H2AX-GFP expression mark high levels of the endogenous gene. Apparently, methylation of the proximal H2AX promoter characterized non-H2AX-GFP expressing cells and was inversely correlated with its H2AX promoter activity. Administration of 5-azacytidine, augmented H2AX promoter activity in a lactogenic hormone- and activated STAT5-dependent manner. In transgenic mice, H2AX-GFP expression picked at pregnancy. The number of H2AX-GFP expressing cells and GFP expression sharply decreased under Stat5a null background and augmented in transgenic mice expressing also the hyperactivated STAT5. Importantly, H2AX-GFP activity was allocated to basal mammary cells which lacked stem cell properties. Conversely, STAT5 hyperactivity activity was detected in their adjacent luminal ones. Taken together, these results suggest a paracrine activation of H2AX via promoter demethylation in specific populations of basal mammary cells by signal(s) from neighboring luminal cells with hyper STAT5 activity. This pathway provides alternative way for the luminaly-confined STAT5 to regulate and affect intracellular processes in the basal mammary cell compartment.

Foxo1 is Involved in Estrogen Receptor Signaling in Pancreatic Beta Cells

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Estradiol-17β (E2) exerts protective effects on pancreatic β-cells through phosphorylation and transcription. The Foxo1 transcription factor plays a major role in β-cell proliferation and differentiation and is tightly regulated by phosphorylation. Interaction of Foxo1 with estrogen receptor α (ER) has been previously shown to influence transcription and cell cycle in classic estrogen responsive tissues but has not been studied in pancreatic β-cells. We therefore examined the effect of E2 on β-cell proliferation in human and rodent models and the role of Foxo1 in E2/ER-mediated induction of proliferation, transcription and phosphorylation.

The effect of E2 on proliferation was assessed in INS1-E (rat insulinoma) cells and human islets by 3[H]-thymidine incorporation into DNA after exposure to E2 and specific agonists to ERα, ERβ and GPER. In INS1-E cells grown under standard conditions all estrogenic agonists induced a ~3 fold increase in proliferation. However, under severe hyperglycemia (glucose 25mM) only the ERα agonist PPT retained a similar proliferative response. In human islets stimulation of all three ERs increased proliferation ~ X2 folds upon mild hyperglycemia (11mM) but upon severe hyperglycemia (25mM) only stimulation of GPER enhanced proliferation (X 2.8 folds). Knock down of Foxo1 expression (by siRNA; 50% reduction) in INS1-E cells abolished E2- and ER-mediated proliferation and attenuated ERα transcription through the ERE (estrogen response element) by 15% ($p< 0.01$), as demonstrated by the luciferase assay. Over- expression of Foxo1 in INS1-E cells increased ERα-mediated transcription through the ERE by 28% ($p< 0.01$). Finally, E2 induced Foxo1 phosphorylation in both rodent and human islets as demonstrated by western blot (~4 fold increase in pFoxo1/Foxo1 ratio, $p<0.05$).

Our findings suggest that in pancreatic β-cells E2 can signal and affect proliferation through alternative ER subtypes depending on the glycemic level. We also provide novel evidence for an E2-Foxo1 pathway in β-cells.

Involvement of MEK5/ERK5 in the Regulation of Nrf2 Functional Activity and Differentiation of Acute Myeloid Leukemia Cells Induced by 1,25-Dihydroxyvitamin D_3

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Differentiation therapy of acute myeloid leukemia (AML) with the hormonal form of vitamin D, 1,25-dihydroxyvitamin D_3 (1,25D), is a promising alternative to standard chemotherapy which is inefficient for the majority of patients. However, 1,25D concentrations required to induce terminal differentiation of AML cells cause severe hypercalcemia. We have shown that the plant polyphenol carnosic acid (CA) enhances the differentiation activity of low doses of 1,25D, and that this enhancement is mediated by the Nrf2/Antioxidant response element (Nrf2/ARE) transcription system. Notably, 1,25D was found to potentiate the CA activation of Nrf2/ARE; however, the mechanism of this action remains unclear. Here, we tested the hypothesis that the MAPK ERK5, which is activated by 1,25D in AML cells, mediates the regulatory effect of 1,25D on Nrf2/ARE in HL60 and U937 human AML cells. Using the reporter gene assay, we found that the MEK5 inhibitor BIX 02189 moderately reduced CA-induced ARE transactivation and eliminated the 1,25D enhancement of this effect. In contrast, the ERK5 inhibitor XMD 8-92 strongly potentiated ARE activation by CA, without altering the 1,25D effect. Similar opposing actions of BIX 02189 and XMD 8-92 were also observed when measuring the protein expression of Nrf2 and its downstream gene products (heme oxygenase-1 and thioredoxin reductase-1). The CA enhancement of 1,25D-induced cell differentiation was accompanied by synergistic upregulation of the vitamin D receptor (VDR) protein levels. While XMD 8-92, but not BIX 02189 further strengthened the differentiating activity of 1,25D+CA, neither inhibitor had an additional effect on VDR expression. Moreover, only XMD 8-92 had an ability to cooperate with CA in the induction of differentiation, even in the absence of 1,25D. Overall, these results suggest that MEK5 and ERK5 are differentially involved in regulatory processes controlling maturation of AML cells and may represent novel targets for differentiation therapy of this devastating disease.

Targeting IGF-1R in Breast Cancer: Combined Treatment With Conventional Chemotherapeutic Drugs

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Most tumors, including breast cancers, express high levels of IGF-1 receptor (IGF-1R) mRNA and protein. IGF-1R activates two main downstream pathways - survival and proliferation. Cancer cells depend on the survival pathways to overcome death signals induced by cytotoxic chemotherapy. We postulate that inhibition of survival pathways through IGF-1R targeting simultaneously with cytotoxic chemotherapy would result in a synergistic growth inhibitory effect.

To evaluate this hypothesis, two malignant breast cancer cell lines, MCF7 and BRCA1-null HCC1937, were treated with a panel of standard chemotherapeutic drugs as a single agent or in combination with AEW541, a selective IGF-1R tyrosine kinase inhibitor. Cell proliferation was measured by XTT assays.

The combined treatment of AEW541 and chemotherapy synergistically inhibited the growth of MCF7 cells, however, no synergy was observed in HCC1937 cells.

To evaluate the hypothesis that IGF-1R inhibition is effective only in cells which depend on IGF-1R signaling and, most probably, over-express the receptor, we compared IGF-1R levels in both cell lines. As expected, MCF7 cells express high level of IGF-1R, while HCC1937 express very low IGF-1R level. Thus, combination of IGF-1R inhibitor and chemotherapy was highly synergistic in cells expressing high level of IGF-1R, but not in cells with low IGF-1R level.

In summary, our results suggest that IGF-1R targeted therapy should rely on the use of IGF-1R as a biomarker. Moreover, combined treatment with IGF-1R inhibitor and chemotherapeutic drugs can greatly improve the treatment efficiency in breast cancer patients whose tumor cells express high IGF-1R level.

Healing a Failing Heart: a Novel Anti-Apoptotic Role of StAR Expressed in Tissue Repairing Cardiac Fibroblasts

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Steroidogenic acute regulatory (StAR) protein is indispensable for steroid hormone synthesis in steroidogenic cells of the adrenal cortex and the gonads. We have recently reported that StAR is also expressed in the left ventricle of mouse heart following experimental myocardial infarction (MI). Surprisingly, the MI-induced StAR expression rises in the absence of *de novo* steroid synthesis. Spatio-temporal analyses of the post-MI heart showed that StAR expression is restricted to cell types participating in the inflammatory phase of the healing infarct. Studies of cardiac fibroblasts put in culture suggest that StAR endows the cells with anti-apoptotic robustness, a quality that probably allows them to survive the detrimental infarct environment and launch the life-saving healing process. The anti-apoptotic nature of StAR was also analysed in heterologous cell model, where loss-of-function human StAR mutants failed to prevent the apoptotic fate of HeLa cells exposed to a strong apoptogen, staurosporine. Interestingly, the survival activity of StAR requires a supply of plasma membrane (PM) cholesterol; time-lapse confocal imaging methodologies showed that the consequence of StAR expression is a marked depletion of PM cholesterol content, visualized by digitonin assay that inflicts cell permeabilization in a PM cholesterol-dependent manner. Similar conclusions were drawn in view of the inhibited uptake of cholera toxin subunit B, long known to undergo internalization via cholesterol-rich caveolar rafts of the PM. Finally, blocking the availability of PM cholesterol impaired StAR ability to confer the anti-apoptosis robustness. In conclusion, we currently hypothesize that cardiac fibroblasts recruited to the infarct site gain anti-apoptotic resilience when induced to express StAR that allows their survival throughout the post-infarct inflammatory phase. The crucial consequence of StAR expression is thus enabling the cells to enter the reparative phase of proliferation and differentiation to myofibroblast engaged in healing of the damaged myocardium.

CD24 Cell Surface Expression In Mammary Cancer Cells Overexpressing C-myc/VEGF Serves As a Biomarker For Sensitivity To Anti-IGF1R Therapy

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Introduction: The pro-tumorigenic effects of the insulin-like growth factor receptor (IGF1R) are well described. IGF1R promotes cancer cell survival and proliferation and prevents apoptosis, additionally it was shown that IGF1R levels are significantly elevated in most common malignancies including breast cancer. However, results from phase 3 clinical trials in unselected patients demonstrated lack of efficacy for anti-IGF1R therapy. These findings suggest that predictive biomarkers are greatly warranted in order to identify patients that will benefit from anti-IGF1R therapeutic strategies.

Methods: Using the delivery of shRNA vectors, we tested the role of the IGF1R in the development of mammary tumors. Based on CD24 cell surface expression, control and IGF1R-knock down (IGF1R-KD) cells were FACS sorted into $CD24^-$ and $CD24^+$ subsets and further characterized in-vitro. The tumorigenic capacity of each was determined following orthotopic inoculation into the mammary fat pad of female mice. Tumor cells were FACS characterized upon sacrifice to determine IGF1R effect on the plasticity of this cell's phenotype. Metastatic capacity of the cells was assessed using the tail vein assay.

Results: Down-regulation of the IGF1R specifically in $CD24^+$ cancer cells affects both their morphology and phenotype in-vitro. Moreover, we demonstrate that IGF1R-KD abolished $CD24^+$ cells capacity to form mammary tumors and metastasis. Moreover,both $CD24^+$/IGF-1RKD cells and tumors showed a significant reduction of SLPI (tumor promoting gene) expression.

Moreover, we demonstrate that the IGF1R is essential for the maintenance of stem/progenitors-like phenotype, furthermore, IGF1R-KD induces in-vivo differentiation of the $CD24^+$ cells toward the $CD24^-$ phenotype. This supports the anti-tumorigenic effects of IGF1R-KD, as we recently published that these differentiated cells demonstrate significantly lower tumorigenic capacity compared with their $CD24^+$ counterparts.

Conclusion: These findings suggest that CD24 cell surface expression may serve as a valuable biomarker in order to identify mammary tumors that will positively respond to targeted IGF1R therapies.

Stem Cells & Pituitary Development

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During morphogenesis, embryonic tissue progenitors proliferate, differentiate and are organised, via cellular interactions, in tri-dimensional organs. In the adult most organs retain a cell population sharing essential properties with embryonic progenitors, fundamentally the ability to self-renew and differentiate to give rise to the specialised cell types comprised in the organ in which they reside. These characteristics define them as adult stem cells (SCs). It is important to characterize SCs to better understand mechanisms of tumorigenesis, as adult tissue stem cells can give rise to cancer stem cells, and also for regenerative medicine, because SCs can be transplanted, or manipulated *in vivo* to restore missing cells.

The HMG box transcription factor SOX2 is expressed in different populations of embryonic progenitors and adult SCs. In humans and mice, *SOX2*/*Sox2* heterozygous mutations are associated with hypopituitarism [1]. The protein is expressed in the pituitary anlagen or Rathke's Pouch (RP). Its expression is down-regulated as RP progenitors differentiate, but a population of $SOX2^{+ve}$ cells, representing adult pituitary stem cells, persist until adulthood [2-4]. In the developing pituitary, SOX2 is initially required for progenitor proliferation [5]. In addition, we have recently uncovered that it is specifically required for melanotroph emergence. These results show that SOX2 is sequentially required for progenitor proliferation and lineage specification in the developing pituitary.

In the adult, under normal physiological conditions, $SOX2^{+ve}$ pituitary SCs proliferate and differentiate very little [2-4], suggesting that cell turnover relies on endocrine cell division, as demonstrated for corticotrophs [6]. However, it had been known for some time that ablation of the adrenals and/or gonads trigger a transient mitotic wave in non-endocrine cells in the gland, followed by generation of increased number of endocrine cells, those normally regulating the ablated organ [7]. We performed lineage-tracing experiments after pituitary target organ ablation and demonstrated that pituitary SCs both proliferate and differentiate, establishing their regenerative potential [3]. Therefore, pituitary SCs can be mobilized and could be potentially used to modulate endocrine output and treat deficits.

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AR2: a Passe-Partout for Regeneration, Transdifferentiation, and Death in Diabetes and Much More

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Sensing cellular damage by neighboring cells is critical to developing therapies to enhance tissue regeneration. Type I diabetes is an autoimmune disease in which an immune response to pancreatic beta-cells results in their loss over time. While the common view is that this loss is due to autoimmune specific destruction, we present evidence of an additional process in which autoimmunity promotes islet-cell transdifferentiation, ending with a large excess of delta-cells, resulting from alpha- to beta- to delta-cell transdifferentiation process. Intermediates in the progress of islet cell transdifferentiation were identified in murine and human type I diabetes. Here, we report that the molecular mechanism for this requires activating Protease-Activated Receptor-2 (PAR2), a G-protein-coupled receptor (GPCR). PAR2 was sufficient in the context of severe beta-cell deficiency to induce efficient induction of alpha- to beta- to delta-cell transdifferentiation in a manner very similar to what occurred in type I diabetes as demonstrated by genetic lineage-tracing mice together with time course analysis. Islet transdifferentiation proceeded in an islet autonomous manner, indicating the existence of a sensing mechanism that controls transdifferentiation within each islet. In addition to transdifferentiation, PAR2 regulated beta-cell apoptosis in pancreatitis. The finding of evidence for islet cell transdifferentiation in rodent and human type I diabetes and its induction by a cellular receptor in a model of type I diabetes has important implications for the development of beta-cell regeneration therapies for diabetes.

2015 Thyroid Nodule and Cancer Guidelines - What's New?

Eyal Robenshtok
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The newly released thyroid cancer treatment guidelines from the American Thyroid Association (ATA) offer extensive recommendations for the management of thyroid nodules and differentiated thyroid cancer (DTC). The guidelines include 101 recommendations, and present many important changes from the 2009 guidelines including: new indications for thyroid nodules biopsy, molecular testing for patients with indeterminate cytology, changes in surgical approach (more hemithyroidectomies), more selective use or radioiodine, new systemic therapies, and more.

In our talk today, we'll discuss the reasons for the extreme depth of coverage and level of detail for each recommendation, and will focus on recommendations which will most dramatically impact our day-to-day practice.

Management of Congenital Adrenal Hyperplasia During Pregnancy - Optimizing Outcomes

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Non-classical 21 hydroxylase deficiency (NC21OHD) is a mild form of congenital adrenal hyperplasia presenting with various degrees of postnatal virilization. Mild mutations of the *CYP21A2* gene coding for the steroid 21OH enzyme produce enzymatic activity ~20-50% of normal, thus slightly impairing cortisol synthesis and leading to increased androgen levels. NC21OHD is common among Ashkenazi Jews (1:400). Untreated adolescents and young women with NC21OHD may present with hirsutism, amenorrhea (primary or secondary), chronic anovulation, and infertility. Androgen excess impairs hypothalamic sensitivity to progesterone, resulting in persistent rapid gonadotropin-releasing hormone pulse frequency, which is associated with luteinizing hormone (LH) hypersecretion and polycystic ovarian syndrome (PCO). Excessive ovarian androgen secretion intensifies the consequences of excessive adrenal androgen production. In order to facilitate conception, both progesterone and androgen levels need to be normalized to early follicular phase levels.

Previous studies reported a higher rate of miscarriages among females with NC21OHD who were not treated with glucocorticoids (GC) before and during pregnancy compared to GC-treated females with NC21OHD. We recently found a higher rate of miscarriages among NC21OHD females compared to Israeli non-NC21OHD controls but no significant difference in the rate of miscarriages and live births among GC-treated and untreated pregnancies. Notably, GC therapy significantly shortened the time to conceive, therfore it is reasonable to administer it to hyperandrogenic NC21OHD women who wish to get pregnant. Thirty percent of our NC21OHD subjects were diagnosed as having PCO compared to 5-10% of women in the general population. The NC21OHD women with concomitant PCO had significantly higher rates of miscarriages compared to the NC21OHD women without PCO. There is a significant increase in placental corticotropin-releasing hormone production leading to increased hypothalamic-pituitary-adrenal axis activity in the second half of a normal pregnancy. In contrast, we documented a decrease in GC needs during NC21OHD pregnancies.

GIP - a Linker between the Metabolic and Immunologic Systems

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Background: We have shown that treatment with a GIP analogue reduces high fat diet (HFD)-induced visceral adipose tissue (VAT) inflammation, as manifested by reduced numbers of infiltrating inflammatory immune cells, attenuated production of pro-inflammatory mediators, and a better metabolic profile. Others have demonstrated that S100A8/9-mediated NLRP3 inflammasome activation in adipose tissue macrophages (ATM) drives the pathological communication between adipose tissue and bone marrow (BM) through IL-1β-instructed myelopoiesis.

Methods: We utilized the BM chimerism approach to target GIPR-deficiency to immune cells and explored the role of GIP in immune cell and NLRP3 inflammasome activation. Both wild type BM reconstituted mice and GIPR-deficiency mice were fed with HFD and were subjected to extended metabolic and immunologic analysis. Complimentary ex- vivo experiments were performed in human VAT tissue harvested during bariatric surgeries.

Results: We show that GIP treatment attenuates expression of S100A8 and IL-1b in VAT of HFD-fed mice. ATM sorted from HFD-fed mice expressed a functional GIP receptor (GIPR) and exhibited reduced expression of S100A8 and IL-1β in response to GIP. Moreover, ATM sorted from VAT of GIP-treated mice had reduced levels of S100A8 and NLRP3. Targeting GIPR deficiency to immune cells using BM chimerism approach resulted in significant VAT myelopoiesis and specifically increased neutrophilia and monocytosis. Expression of CCL2, S100A8, NLRP3 and activated caspase 1 are significantly higher in VAT of mice reconstituted with *Gipr*$^{-/-}$ BM. Concomitantly with the intensified VAT-inflammation, targeting of GIPR-deficiency to immune cells resulted in aggravated metabolic phenotype as manifested by a profound increase in body weight and VAT mass, larger adipocyte cell size, greater systemic insulin resistance and higher liver steatosis, despite similar food consumption. Finally, ex-vivo treatment of human VAT explants with GIP reduced the expression of IL-1β.

Conclusions: we suggest that GIP negatively regulates S100A8/9-induced NLRP3 inflammasome activation in ATM and the downstream BM myelopoiesis. In addition, GIP favorably regulates whole body energy homeostasis and insulin sensitivity by its direct effect on ATM function.

Regulation of growth and metabolic homeostasis by the novel histone like protein Heterochromatin Protein 1 Binding Protein 3 (HP1BP3)

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The Edmond and Lily Safra Center for Brain Sciences

The Alexander Silberman Institute of Life Sciences

The Hebrew University of JerusalemMuch of the difficulty in understanding and treating metabolic disorders arises from the complex interplay of genetics and environment in defining the individual risk of disease. A key process at the crossroads of these two major factors is epigenetic regulation, which integrates genetic predisposition with environmental influence. In this work we identified and characterized a novel protein implicated in chromatin structure and epigenetic regulation named HP1BP3. Deletion of HP1BP3 in a knockout (KO) mouse model had a profound effect, and only 40% of the KO mice survived to adulthood. Furthermore, surviving mice are proportionate dwarfs, with reduction in body weight, body length and organ weight. In addition to their small size, micro-CT analysis showed that *Hp1bp3*$^{-/-}$ mice present a dramatic impairment of their bone development and structure. By three weeks of age, mice of both sexes have severely impaired cortical and trabecular bone, and these defects persist into adulthood and beyond. Primary cultures of both osteoblasts and osteoclasts from *Hp1bp3*$^{-/-}$ bone marrow and splenocytes respectively showed normal differentiation and function, strongly suggesting that the impaired bone accrual is due to non-cell autonomous systemic cues *in-vivo*. One major endocrine pathway regulating both body growth and bone acquisition is the IGF regulatory system, composed of insulin like growth factor 1 (IGF-1), the IGF receptors (IGFR) and the IGF binding proteins (IGFBPs). At 3 weeks of age *Hp1bp3*$^{-/-}$ mice exhibited a 60% reduction in circulating IGF-1 and a four-fold increase in the levels of IGFBP-1 and IGFBP-2. These alterations were reflected in similar changes in the hepatic transcripts of the *Igf1*, *Igfbp1* and *Igfbp2* genes. Collectively, these results suggest that HP1BP3 plays a key role in normal growth and bone development by regulating transcription of endocrine IGF-1 components, and may therefore be involved in the epigenetic regulation of metabolic homeostasis.

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