האגודה הישראלית לאנדוקרינולוגיה IES Israel Endocrine Society

The 43rd Annual Meeting of the Israel Endocrine Society

April 7-8, 2014, Dan Panorama Hotel, Tel Aviv

Program

&

Abstract Book

WELCOME ADDRESS

Dear colleagues;

It gives us great pleasure to welcome you to the Annual Meeting of the Israel Endocrine Society. On behalf of the organizing committee and the president of the IES, we wish you a successful conference.

We would like to thank our distinguished lecturers from abroad, Donald Pfaff, Alan Shuldiner, Randy Seeley, Andrew Hattersley, Sundeep Khosla and Marvin Gershengorn and we wish them a pleasant stay and hope they enjoy our wonderful weather.
This year we have a record number of lecturers and topics. Due to the large number of submissions and lecturers, parallel sessions will be held throughout the meeting days allowing you to choose between sessions. We will also have the prizes session to encourage and emphasize
excellent research.

We would like to thank all those involved in the organization of this meeting, the reviewers and the members of the executive committee for spending many hours making this conference interesting and enjoyable.

Sincerely;

Derek Leroith MD, PhD
Chair - Organizing Committee

Yoav Sharoni, PhD
Co- Chair - Organizing Committee

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פרופ' הנס יוחנן לינדר ז"ל – מילים לזכרו

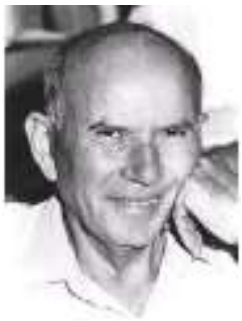
פרופ' הנס יוחנן לינדנר נולד בשנת 1922 בגרמניה ועלה ארצה עם הוריו בשנת 1936. לאחר מלחמת השחרור הוא למד רפואה וטרינארית בסידני (אוסטרליה) וסיים בהצטיינות. את לימודיו לתואר Ph.D. הוא השלים באוניברסיטת קיימבריג' שבאנגליה. עם תום לימודיו, חזר לינדנר לאוסטרליה, התמנה כחוקר בכיר ב-Commonwealth Scientific Research Organization (CSIRO) והתרכז בחקר פיטואסטרוגנים.
בשנת 1964, הגיע ארצה למכון ויצמן כחוקר אורח במח' לביודינמיקה. כעבור שנה הוא קודם לדרגת פרופ' חבר ובשנת 1967 הוא מונה לראשות המחלקה. פרופ' לינדנר בנה מחלקה מולטידיסיפלינארית שעסקה בחקר הפוריות ושינה את שמה ל: "חקר הורמונים". בזכות תכונותיו התרומיות כאינטלקטואל וכמדען, נשא פרופ' לינדנר תפקידים רבים נוספים: הוא מונה במכון ויצמן כדיקן הפקולטה לביולוגיה, לראשות הועדה לקידום מדענים ולוועדה המייעצת של נשיא המכון. בנוסף לכך, הוא היה חבר בחבר הנאמנים של ביה"ח הדסה בירושלים, היה פעיל בהקמת הפקולטה לווטרינריה ואף היה נשיא האגודה הישראלית לאנדוקרינולוגיה. בתקופת כהונתו החלה מסורת קיום הכנסים השנתיים. פרופ' לינדר היה פעיל גם בארגונים בינל"א: חברת בועדות WHO, של מכון מקס פלאנק בגרמניה, של INSERM בצרפת, של ארגונים אנדוקריניים בינל"א וב-Editorial Board של עיתונים מדעיים. הוענקו לו תארי כבוד במס' אוניברסיטאות בעולם. בשנת 1979 הוענק לו פרס ישראל במדעי החיים והוא נבחר כחבר באקדמיה הישראלית למדעים. בשנת 1982 הוענקו לו פרס רוטשילד בביולוגיה וכמו כן, פרס Axel-Munthe בשטח הביולוגיה של הפוריות. פרופ' הנס יוחנן לינדנר נפטר בשנת 1982 עקב מחלה קשה. כראש המחלקה לחקר ההורמונים הכשיר פרופ' לינדנר דורות של חוקרים בתחום האנדוקרינולוגיה. הפרס ע"ש פרופ' לינדנר הוא הפרס היוקרתי ביותר של האגודה הישראלית לאנדוקרינולגיה. הפרס ניתן לחוקר/ת, מתחת לגיל 50 עבור הישגים מדעיים בתחום האנדוקרינולוגיה במהלך חמש השנים האחרונות.

זוכי פרס לינדנר

1989 – ישראל חנוקוגלו
1990 – מרדכי ליסקוביץ
1991 – ראובן רייך
1992 – אבי קרסיק
1993 – רוני זגר
1994 – עירית גרנות
1995 – אורי פלס
1996 – דורית אהרוני
1997 – חנה קנטי
1998 – בנימין גלזר
1999 – מיכל נאמן
2000 – רינה מידן
2001 – חיין ורנר
2002 – משה פיליפ
2003 – שרה פרבר
2004 – פואד פארס
2006 – איתן גרוס
2007 – אילן שמעון
2008 – חגית אדלר-פינקלמן
2009 – אסף רודיך
2010 – גיל ליבוביץ
2011 – אלון חן
2012 – פיליפה מלמד
2013 – יובל דור

ערן הורנשטיין – 2014

פרופ' ישראל חוברס ז"ל – מילים לזכרו



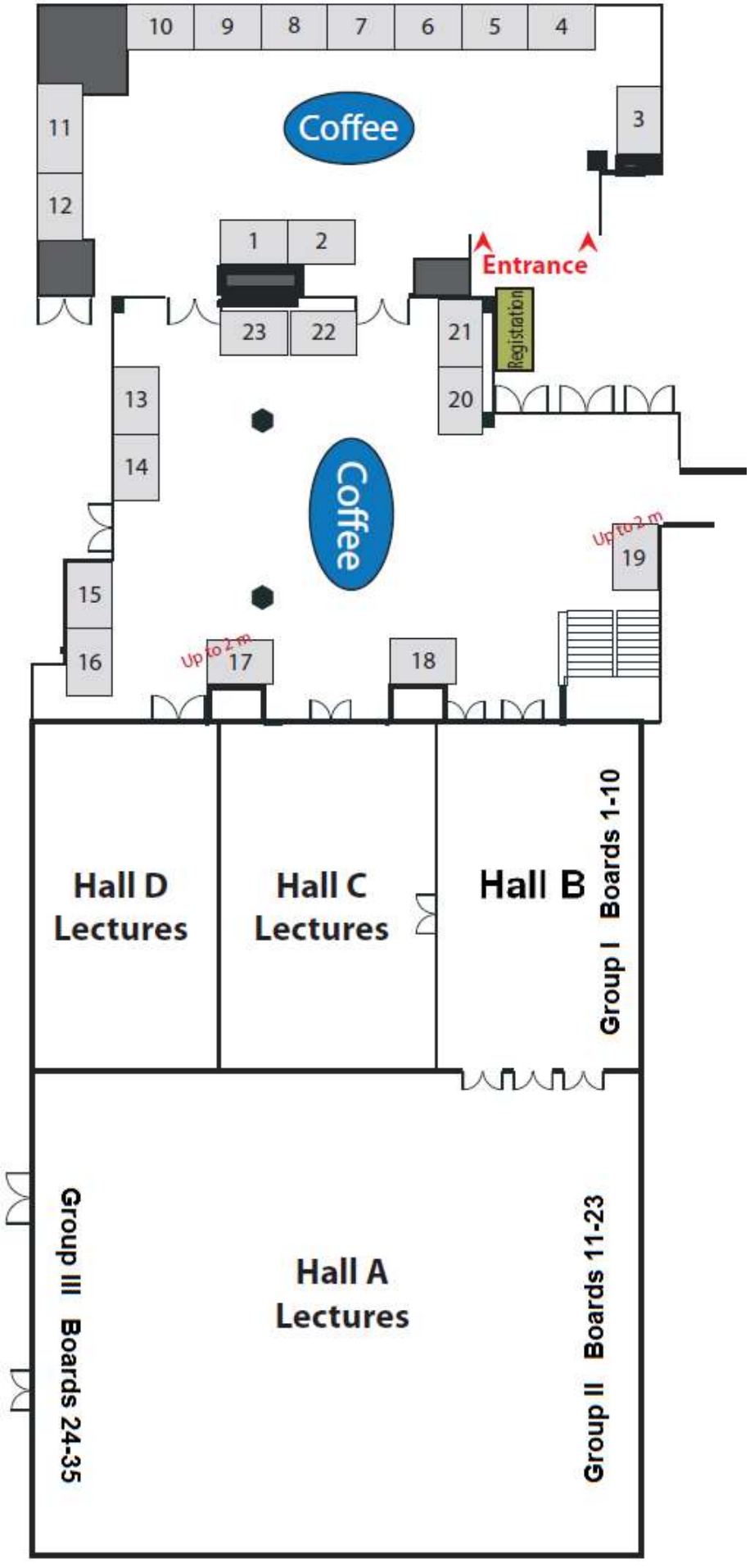
פרופ' חוברס נולד בפולין ב-1923 והגיע לארץ בגיל חצי שנה. את חינוכו היסודי קיבל בביה"ס החקלאי ע"ש מאיר שפיה. הוא היה פעיל במשך תקופה ארוכה בשורות ההגנה, בהבאת יהודים ארצה ובצה"ל. הוא התקבל ללימודי הרפואה בשוויץ, אך בינתיים פרצה מלחמת העצמאות והוא החליט להישאר בארץ ולהשתתף בה באופן פעיל, בעיקר בהגנת איזור 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 – ארף 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

דנה חודרלנד – 2014

CONFERENCE VENUE FLOOR PLAN



Monday, April 7th 2014		
07:30-08:30	Registration	
08:30-10:00	**Symposiums (2 Parallel Sessions):**	
Male Hypogonadism **Hall A**	**Hormones and Brain** **Hall CD**	
Yardena Tenenbaum-Rakover: "Hypogonadotrophic Hypogonadism"	Donald W. Pfaff: "Effects of Hormones on Histone Modifications in the Brain"	
Haim Pinkas: "Assisted Reproductive Technology (ART) for Male Infertility"	Tali Kimchi: "The Mechanism Underlying Parental Care in Males and Females"	
Naftali Stern: "Testosterone Replacement Therapy: To Be or Not to Be"	Shlomo Wagner: "Oxytocin, Vasopressin and Long-Term Social Recognition Memory"	
10:00-10:30	Coffee Break and Exhibition	
10:30-10:45	**Opening Remarks: Eddy Karnieli and Derek LeRoith** **Hall A**	
10:45- 11:30	**Plenary Lecture 1 - Hall A Personalized Medicine and Pharmacogenomics of Diabetes and Related Traits: Real-world Challenges in Translation to Clinical Practice** ***Alan Shuldiner***	
11:30-13:00	Guided Poster Session **Halls A,B**	
13:00-14:00	Lunch	
14:00-14:45	**Plenary lecture 2 - Hall A A Bariatric Surgery: It's not What You Think it is** ***Randy J. Seeley***	
14:45-15:15	**Coffee Break**	
15:15-16:45	**Short Oral Presentations (Parallel Sessions)**	
Diabetes and Obesity **Hall A**	**Hormones, Growth Factors & Cancer** **Hall C**	**Reproduction** **Hall D**
16:45-17:45	**Meet the Professor / Expert (2 parallel sessions):**	
Alan Shuldiner: Personalized Medicine for Diabetes and its Complications: The Future is Now **Hall A**	Sophia Ish-Shalom: *Hypoparathyroidism- Diagnostic and Therapeutic Dilemmas* **Hall C**	

Tuesday, April 8th 2014			
07:30-08:30	Registration		
08:30-10:00	**Short Oral Presentations (Parallel Sessions)**		
Thyroid/Adrenal **Hall A**	**Signal Transduction and vitamin D** **Hall C**	**Bone Metabolism / Steroids** **Hall D**	
10:30-10:00	Coffee Break and Exhibition		
10:30-12:00	Symposiums (2 Parallel Sessions):		
Neonatal Diabetes *Sponsored by Novo Nordisk* **Hall A**		**New Horizons in Diabetes and Obesity** **Hall CD**	
Andrew Hattersley: "From Base Change to Better Care in Neonatal Diabetes"		Yuval Dor: "Glucose control of pancreatic β -cells"	
Case presentations: Ronen Spiegel: "RFX6 a Novel Cause of Syndromic Neonatal Diabetes" *Amnon Zung*: "Permanent Neonatal Diabetes Mellitus due to Kir 6.2 Activating Mutation: A Long Term Follow-up" *Revital Nimri*: "The Spectrum of Neonatal Diabetes at a Tertiary Center: The Neurologic Enigma"		Assaf Rudich: "Autophagy, Stress, and the Fat-Liver Axis in Obesity" *Haim Cohen:* "Regulation of Healthy Lifespan by SIRT6"	
12:00-13:30	**Prizes Session and IES Members Assembly Meeting** **Hall A**		
13:30- 14:30	Lunch		
14:30- 15:15	**Plenary Lecture 3 –** **Hall A** **Update on Treatment of Osteoporosis- Sundeep Khosla**		
15:15- 15:30	**Coffee Break**		
15:30-17:00	Symposiums (2 Parallel Sessions):		
Adrenal **Hall A**		**G Protein - Couple Receptors in Endocrine Processes** **Hall CD**	
Ofer Beniaminov: "How Accurate Can Adrenal Imaging Be in Predicting Malignancy?"		Marvin Gershengorn: "Targeting the Human TSH Receptor – Novel Probes for Assessing TSH Physiology and Lead Drugs for Thyroid Diseases"	
Petachia Reissman: "The Surgical Approach to the Suspicious Adrenal Mass"		Rachel Bar-Shavit: "Protease-Activated-Receptors: PARtners in Physiological and Pathophysiological Processes"	
Grattiana Herman: "The Weiss Criteria for the Diagnosis of Adrenal Cortical Carcinoma in the Era of Molecular Markers"		Masha Niv: "G-Protein Coupled Receptors and Their Ligands: Selectivity and Promiscuity"	
Asher Salmon: "The Medical Approach to Adrenocortical Carcinoma"			
17:00-18:00	**Meet the Professor**		**Hall CD**
Eli Hershkovitz: RICKETS UPDATE 2014			

Hypogonadotrophic Hypogonadism

Yardena Rakover

Pediatric Endocrinology Unit, Haemek Medical Center

Assisted Reproductive Technology (ART) for Male Infertility

Haim Pinkas

Department of Obstetrics & gynecology, Rabin Medical Center, Beilinson Hospital

Subfertility is a condition found in up to 15% of couples of reproductive age and until the late 1970s, there were few options for treating these couples. Since the first successful in vitro fertilization (IVF) was described, the efficacy of subfertility treatment has greatly improved. However, the technique had great limitations in achieving pregnancy in couples with compromised semen parameters. Prior to the availability of assisted reproductive technologies (ART), the use of donor sperm was the only treatment option for these couples. Male factor accounts for almost 50% of infertility causes of the infertile couple. Unfortunately, about 40-60% of the cases are idiopathic. Azoospermia which represents the most severe form of male factor infertility is observed in 1% of the general population and in 15% of infertile men.

Two breakthroughs in assisted reproductive technics have revolutionized the treatment of patients with severe oligo-terato-astenozoospermia (OTA) or azoospermia; enabling men to father genetically own offspring. The first was the development of intracytoplasmic sperm injection (ICSI) technology, published by Palermo (Lancet, 1992). This was a tremendous achievement, resolving the infertility of many men with severe OTA, which otherwise were regarded sterile and were referred to donor insemination treatment. Yet, ICSI could not help patients with azoospermia. The second milestone was the development of testicular sperm retrieval procedures for azoospermic men with non-obstructive azoospermia (NOA). The spermatozoa obtained were then used to inseminate oocytes by ICSI. The first successful pregnancies following testicular sperm extraction were reported by Devroey et al (Human reproduction 1995).

Three testicular sperm retrieval techniques are currently used: TESA/FNA (testicular sperm aspiration/fine needle aspiration), open testicular biopsy; TESE (testicular sperm extraction) and micro-TESE (combined TESE with the assistance of an operating microscope). Ongoing researches carry some hope that stem cells might be manipulated in the future and used to preserve and/or restore the fertility of patients who are not producing sperm.

Testosterone Replacement Therapy: To Be or Not to Be

Naftali Stern

Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Ctr and Sackler Faculty of Medicine, Tel Aviv University

Recent evidence confirms that low testosterone levels are highly prevalent in older men. Likewise low testosterone levels are strongly linked to obesity, the metabolic syndrome, type 2 diabetes mellitus and chronic diseases. Low testosterone has been linked not only to the induction of a cluster of vaguely defined symptoms spanning all the way from fatigue to cognitive alterations but also to increased risk of cardiovascular events and overall mortality. Still, based mainly on observational studies, testosterone replacement therapy in frail and/or elderly subjects may be linked to increased cardiovascular event rate. With this background in mind, testosterone treatment must be carefully individualized in terms of the diagnosis of hypogonadism, particularly late onset hypogonadism (LOH), setting clear treatment goals, selecting a proper treatment mode and designing a well-organized follow up system. Many testosterone assays have unacceptably poor performance and "black box" assays now dominate the market. Free testosterone results and derived androgen indices are often futile since the insertion of highly variable hormone resuts into a uniform equation can do no better than the "mother assays". Mass spectrometry assays will likely improve the available diagnostic tools dramatically. Though not well established, age must be considered not only for the diagnosis of low testosterone, but also for the interpretation of on-treatment levels. It is now appreciated that men vary in terms of androgen response and at least part of this variability is related to CAG repeat number in the androgen receptor. Non-testosterone forms of therapy such as weight loss must be recognized. Though uncommon, hypogondaotropic hypogonadism secondary to organic pituitary disease must be considered when appropriate. Lastly, treating physicians must be aware of the main metabolic pathways of testosterone and the entire array of the biological effects of testosterone and its metabolites so that a rounded, well informed follow up can be offered.

Effects of Hormones on Histone Modifications in the Brain

Donald W. Pfaff

Neurobiology and Behavior, The Rockefeller University

The Mechanism Underlying Parental Care in Male and Female

Tali Kimchi, Niv Scott

Department of Neurobiology, Weizmann Institute of Science

The hypothalamus has a critical role in coordinating sexually dimorphic behaviors upon environmental cues. The hypothalamus contains few sexual dimorphic areas which are different in morphology, density, gene expression and neuronal projections. However, the relationship between sexually dimorphic brain areas and sexually dimorphic behaviors is poorly understood. We focused on hypothalamic dopaminergic neuron population – the anteroventral periventricular nucleus (AVPV), which in females possesses up to 3-fold more neurons than in males. We managed to cause specific and precise alteration of this dimorphic neural population in both males and females adult mice using two different approaches – neurotoxic biochemical agent and viral genetic manipulation. We found that ablation of these sexual dimorphic dopaminergic neurons leads to parental behavioral deficiency in both sexes while up- regulation of the neural population leads to increased maternal behavior. Importantly, we also found that alteration of this neuronal population changed oxytocin (OT) level in blood serum. Last, neuronal tracing, using conditioned viral vector, reveled strong evidence that these dopaminergic neurons project to oxytocinergic neurons in the paraventricular nucleus (PVN).

Oxytocin, Vasopressin and Long-term Social Recognition Memory

Shlomo Wagner

Department of Biology and Department of Neurobiology, University of Haifa

Mammalian social organizations require the ability to recognize and remember individual conspecifics. This social recognition memory (SRM) can be examined in rodents using their innate tendency to investigate novel conspecifics more persistently than familiar ones. SRM is known to be mediated in most mammals by the main and accessory olfactory systems, both of which innervate the medial amygdala (MeA). Multiple studies showed that brain activity of the neurohypophysial hormones oxytocin and arginine-vasopressin is crucial for SRM. We have used the social recognition and social discrimination paradigms to explore the neuronal and molecular mechanisms underlying SRM formation in rats. We found that SRM consolidation into long-term memory was blocked following only one day of social isolation. This impairment could be reversed either by returning the animals back to group-housing or by systemic administration of arginine-vasopressin. We also found that long-, but not short-term SRM depends upon protein synthesis and oxytocin-dependent long-term synaptic plasticity in the MeA. Interestingly, socially isolated rats were deficient in their MeA responses to oxytocin application, suggesting that this deficiency mediate their inability to form long-term SRM. To summarize, our results reveal some of the neuronal, hormonal and molecular mechanisms underlying social recognition memory in rodents.

Plenary Lecture 1

Personalized Medicine and Pharmacogenomics of Diabetes and Related Traits: Real-world Challenges in Translation to Clinical Practice

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Within the last 10 years, there has been an explosion in our knowledge of sequence variation in the human genome and its relationship to health and disease. The genetic causes of more than 3,000 monogenic diseases, including more than 40 monogenic forms of diabetes, are now known. Through genome-wide association analysis, common variants at thousands of loci have been associated with common polygenic diseases and traits, including more than 70 loci for type 2 diabetes. Now more than 100 medications contain pharmacogenomic information in their labeling. Deeper knowledge of the human genome has unveiled new insights into human biology and pathophysiology, and has identified novel drug targets for diabetes, cardiovascular disease, cancer and many other diseases. The goal of personalized medicine is to apply this genomic knowledge to optimize patient care for more individualized and effective treatment and prevention of disease. Despite a substantial evidence base, implementation of personalized medicine and pharmacogenomics into routine patient care has been slow due to a number of non-trivial practical barriers. The mission of the University of Maryland Program for Personalized and Genomic Medicine is to advance discovery in genomics and other "omic" sciences; to accelerate translational research and implementation of these discoveries into more effective and safe individualized health care; and to enhance the training and education of current and future generations of physicians and scientists through a personalized and genomic medicine driven curriculum. Successful examples that will be discussed include discovery of the first null mutation in human APOC3 validating this pathway as a target for novel triglyceride lowering therapies; implementation of CYP2C19 genetic testing for more effective personalized anti-platelet therapy; and the Personalized Diabetes Medicine Program. These examples may prove useful to other institutions as they implement genomic medicine and pharmacogenomics into patient care, a critical step in the pathway to personalized medicine.

Plenary Lecture 2

Bariatric Surgery: It's not What You Think it is

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While various bariatric surgeries provide both the largest and most durable weight loss of any currently available therapy, there remain great uncertainties around the mechanisms that produce such weight loss. At least some surgical approaches also reduce obesity-related comorbidities including type 2 diabetes and hyperlipidemia. These weight and metabolic successes put a premium on understanding how these surgeries exert their effects. We have been using a variety of mouse models to test specific hypotheses about key molecular targets that mediate the benefits of bariatric surgery. Included in these are gut-brain hormones such as GLP-1 and ghrelin which have been widely hypothesized to play a role in the benefits of surgery. Other potential mediators include bile acids and bile acid receptors which are altered both in the lumen and in circulation after bariatric procedures.

Oral Presentations I: Diabetes and Obesity

RNA Binding Protein PTB and MicroRNA-221 Co-regulate AdipoR1 Translation and Adiponectin Signaling

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Adiponectin receptor 1 (AdipoR1) mediates adiponectin's pleiotropic effects in muscle and liver and plays an important role in the regulation of insulin resistance and diabetes. Here, we demonstrate a pivotal role for microRNA-221 (miR-221) and the RNA binding protein polypyrimidine tract binding protein (PTB) in post-transcriptional regulation of AdipoR1 during muscle differentiation and in obesity. RNA-IP and luciferase reporter assays illustrated that both PTB and miR-221 bind AdipoR1-3'UTR and cooperatively inhibit AdipoR1 translation. Depletion of PTB or miR-221 increased, while overexpression of these factors decreased, AdipoR1 protein synthesis in both muscle and liver cells. During myogenesis, downregulation of PTB and miR-221 robustly induced AdipoR1 translation, providing a mechanism for enhanced AdipoR1 protein expression and activation in differentiated muscle cells. In addition, since both PTB and miR-221 are upregulated in liver and muscle of genetic and dietary mouse models of obesity, this novel translational mechanism may be at least partly responsible for the reduction in AdipoR1 protein levels in obesity. These findings highlight the importance of translational control in regulating AdipoR1 protein expression and adiponectin signaling. Given that adiponectin is reduced in obesity, induction of AdipoR1 could potentially enhance adiponectin beneficial effects and ameliorate insulin resistance and diabetes.

Type 1 Diabetes Mellitus Presented with Diabetes Ketoacidosis: Prevalence by Different Demographic Variables

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Background: Diabetic ketoacidosis (DKA) is the leading cause of death in children and adolescents with Type 1 Diabetes Mellitus (T1DM). Despite an increase in the disease prevalence, there has not been any reduction in the rate of DKA over the past years.

Objective: To examine the epidemiology of DKA at presentation of T1DM in Israel and determine prevalence and risk factors.

Methods: Data collected from the national registry at The Gertner Institute, including children (0-17 years) who were diagnosed between 2004-2008. In addition, a retrospective chart review of subjects with T1DM from three medical centers in Israel was conducted.

Results: The study included 1450 cases from the national registry and 438 cases from the three medical centers. The rate of DKA was steady at around 39%. Demographic variables that were found to be associated with DKA at diagnosis were: 1. Young age- DKA was significantly more common among children under 6 years of age compared to 6-10 years and 11-18 years (47% vs. 39% vs. 35%, respectively, p0.01); 2. Maternal Ashkenazi origin was found to be a protective factor (OR 0.43, p=0.04); 3. The rate of DKA was 49% in Jerusalem area, 41% in northern Israel, 36% in central Israel and 34% in southern Israel (P=0.04); 4. DKA at presentation was significantly less common with first degree relative with T1DM compared to none (22% vs. 41% respectively, p0.01).

Conclusions: The study identified risk factors for DKA as presentation in Israel. Increasing the knowledge among population at risk about symptoms and signs of diabetes may allow earlier detection of T1DM and prevention of DKA at presentation.

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Lean Mass Loss during the Metabolic-syndrome Treatment has Unfavorable Cardiovascular Effects Negating Benefits Attained by Fat Mass Loss

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Intentional weight loss induces favorable cardiovascular (CV) effects secondary to fat mass reduction. However, the CV impact of reduction in lean body mass, which often accompanies weight loss, has not been explored. Muscle disintegration could elicit inflammation with adverse systemic effects, potentially affecting the vasculature.

Aims: To examine the relationship between lean/ fat mass loss, blood pressure (BP) and intima-media thickness (IMT) during 1 year of exercise/diet treatment in patients with the metabolic syndrome (MetS).

Methods: Thirty eight subjects with MetS participated in a multidisciplinary program targeting all known risk factors with emphasis on diet and exercise. Carotid intima media thickness (IMT), 24h ambulatory BP monitoring (ABPM), central BP and body composition by DEXA, were evaluated before the intervention and 1 year later.

Results: Predictably, men with larger fat mass reduction (12.5%) enjoyed significant reduction in ABPM systolic pressure (-11 mmHg; p0.03). However, compared to men showing good muscle preservation (gain or loss2.9% in lean mass) men with notable lean mass depletion (2.9%) showed (1) no decline in central systolic BP (+2mmHg vs. -21mmHg; p0.0033); (2) no reduction in IMT (+54um vs. -29um; p0.033). Likewise, women with significant lean mass loss showed no decline in mean ABPM diastolic pressure.

Conclusions: The loss of lean body mass during treatment of the MetS is associated with negative effects on BP and IMT, particularly in men. This novel association should draw attention to the possibility that muscle preservation may be important for cardiovascular outcome during intentional weight loss.

Novel Human Resistin Mutant that Acts as Resistin Antagonist Attenuates Insulin Resistance and Reduces Body Weight in HFD-fed Mice.

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Resistin is a cysteine-rich 12.5-kDa polypeptide secreted by adipose tissue in rodents and by macrophages in humans acting as covalent dimer which is formed by formation of a single disulfide bond between two monomers promoting inflammation and insulin resistance. To block the undesired actions of resistin we have invented and purified to homogeneity recombinant human resitin mutant that acts as resistin antagonist (RA). The purity of the lyophilized mutant was evidenced by SDS-PAGE and by SEC analyses. In vitro experiments were carried out in SH-SY5Y human non-differentiated and differentiated neuroblastoma cells and in hypothalamic mouse cell line. Resistin phosphorylated both AKT and ERK 1/2 in dose dependent manner in the 3 cell lines and phosphorylation of both AKT and ERK 1/2 were gradually attenuated by 5 to 100 excess of RA, whereas RA alone was devoid of ability to phosphorylate those proteins. Male C57BL/6 mice fed HFD for 6 weeks gained significantly more weight compared to chow-fed animals. Following the two-weeks treatment with RA the HFD-fed mice lost ~ 2.5 gram of their weight, mostly attributed to decreased visceral fat pad size. In contrast RA treatment had no effect in chow-fed mice. RA treatment also normalized the glucose tolerance of HFD-fed mice to the levels observed of chow-diet fed mice as evidenced by ip GTT and ITT. In conclusion, our above described experiments clearly indicate that RA inhibits resistin action in cell cultures and attenuates obesity and insulin resistance in mice fed high fed diet.

Inhibition of Diabetic Cataract by Glucose Tolerance Factor (GTF) Extracted From Yeast

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Diabetes is associated with a higher prevalence of cataract. Hyperglycemia induces glycation of lens proteins leading to generating ROS and oxidative stress, reducing antioxidant activity and elevating polyol accumulation, causing a development of cataract.

The purpose of the present study was to investigate the damage caused by high glucose to the eye lens and to examine the anti-diabetic agent, Glucose Tolerance Factor (GTF), extracted from yeast, as anti-cataractogenic factor both in vivo and in vitro.

Streptozotocin diabetic rats were divided to untreated group and to a group treated orally with 15 daily doses of GTF. Cataract formation was observed in untreated diabetic animals whereas in the eyes of diabetic rats treated with GTF ctaractogenesis was inhibited.

Bovine lenses were incubated in vitro for 14 days. The lenses were divided into four groups: (1) Control (2) Lenses incubated in high glucose (450mg%) medium (3) Control lenses incubated with GTF (4) Lenses incubated in high glucose (450mg%) medium with GTF.

An automated scanning laser system monitored lens optical quality. Lens epithelial samples were taken daily for enzymes analysis.No change in the optical quality of control lenses was observed during the culture period. Lenses incubated in high glucose medium showed reduction in optical quality. GTF decreased the damage caused by high glucose. The enzymatic activity of Na/ K ATPase, and Aldose reductase (AR) in lens epithelial cells was affected by high glucose level. GTF partially prevented the adverse enzymatic changes. Our findings present GTF as an anti cataractogenic material.

High Risk of Diabetes Mellitus [DM] in Ethiopian Jewish Immigrants to Israel: The Effect of Lifestyle Changes may Differ by Age at Occurrence

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The prevalence of DM in Ethiopian Jewish Immigrants [EJI] was 0.4% on arrival in Israel and has been increasing ever since.

We aimed to compare DM risk among EJI and non-Ethiopian Jews [NEJ] living in the same geographical area in Israel; and assess whether differences in DM risk between the two ethnic groups are explained by differences in baseline levels of the metabolic syndrome [MetS] components. Data on baseline levels of the MetS components and DM incidence between 2008 and 2011 were retrieved for 7,722 EJI and 14,683 age- and sex-matched NEJ. Sex-adjusted hazard ratios [HRs] for DM were calculated in selected age-groups, and further adjusted for the MetS components.

The 4y DM risk was 3.6%, 15.2%, 14.8% for EJI and 2.1%, 11.8%, 17% for NEJ, in the 50y, 50-60y,≥60y age-groups, respectively. Compared to NEJ, EJI had significantly greater DM risk in the 50y and 50-60y age groups. DM risk in people 60y did not differ by ethnicity, implying a possible birth cohort effect (see table). Adjustments for MetS components except BMI did not materially change the HR estimates, while BMI adjustment increased them, implying that differences in BMI or MetS components do not explain the difference in risks between the two communities.

The effect of lifestyle changes associated with immigration on DM risk may differ by age at change occurrence.

Table: DM Risk in EJI vs. NEJ in 3 age-groups

	Age <50y	Age 50-60y	Age ≥60y
n [EJI / NEJ]	6,029/11,244	725/1,533	968/1,906
Model	Hazard ratio (95% confidence interval); Reference group: NEJ		
Sex-adjusted only	1.81 (1.50 , 2.17)	1.36 (1.07 , 1.73)	0.89 (0.73 , 1.08)
Plus Triglycerides	1.95 (1.62 , 2.35)	1.34 (1.05 , 1.70)	0.87 (0.72 , 1.07)
Plus Body Mass Index	2.31 (1.91 , 2.79)	1.55 (1.22 , 1.98)	1.02 (0.83 , 1.24)
Plus HDL Cholesterol	1.84 (1.53 , 2.22)	1.30 (1.03 , 1.66)	0.87 (0.71 , 1.06)
Plus Systolic Blood Pressure	1.72 (1.43 , 2.07)	1.34 (1.05 , 1.70)	0.90 (0.73 , 1.09)

Identification of Tumor Protecting Pathways in Laron Syndrome Patients

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Laron syndrome (LS) is a human genetic disease that is caused by molecular defects of the growth hormone (GH) receptor (GHR) gene, or post-receptor pathways. The molecular defect in LS leads to GH insensitivity and, consequently, congenital IGF1 deficiency. Overexpression of IGF1 or its receptor is a typical hallmark of most pediatric and adult tumors. Recent epidemiologic studies reported that patients with congenital IGF1 deficiency have a reduced risk of cancer development. The aim of our study was to identify genes and pathways associated with protection of LS patients from cancer.

Epstein-Bar virus-immortalized human lymphoblastoid cell lines from LS patients, relatives, and normal controls were used in this study. Expression levels of receptors, cytoplasmic mediators and activation of signaling cascades were measured by western immunoblotting. Genome-wide profiling analyses were conducted using RNA obtained from patients and controls. Microarray data was validated by RQ-PCR.

Western blot analysis revealed that LS-derived lymphoblastoids express higher levels of tumor suppressors, than relatives. On the other hand, levels of positive cell cycle regulatory proteins were reduced in LS patients. Microarray analysis revealed that genes involved in the control of cell cycle, motility, growth and differentiation were down-regulated in LS compared to controls. Finally, annexin V staining analysis showed that cells from LS patients have a higher apoptosis rate compared to controls.

Our preliminary analyses provide evidence that proteins associated with tumor suppressive, pro-apoptotic pathways are overrepresentated in LS patients whereas proteins involved in proliferative events are underrepresented.

The Highly Specific Role of the Insulin Receptor in Breast Cancer Growth

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Recent data accumulated from clinical trials showed that specific IGF-1R targeting is not effective as a treatment for breast cancer. One possible reason is that the IR may deliver mitogenic signals independently or as compensation to the IGF-1R inhibition. Here we aim to isolate the IR and the IGF-1R role in mediating breast tumor progression in both WT mice and the unique hyperinsulinemic MKR mice. First, we induced, individually IR and IGF-1R knock-down (KD) in the mammary carcinoma Mvt-1 cell line. Surprisingly, IGF-1R-KD cells responded well to IGF-1 stimulation. Using the specific IR antagonist-S961, we demonstrated that IR inhibition significantly reduced IGF1R-KD cells response to IGF-1 stimulation. In-vivo results demonstrated that tumor growth was significantly reduced only following IR-KD cells injection, in comparison with the control cells in both WT and MKR mice. Encouraged by the small tumors observed by the IR-KD cells, we looked for a correlation between IR and CD24 that was just recently suggested as a prognostic marker for breast cancer. FACS analysis of CD24 expression in the IR-KD cells revealed more than 60% decrease in CD24 expression, compared to the control cells. To investigate if high CD24 expression can restore tumorigenicity of the IR-KD cells, we sorted the IR-KD cells into IR-KD/CD24- and IR-KD/CD24+ cells; our results indicate that CD24 can partly but significantly restore tumorigenicity capacity of IR-KD cells.

Taken together, our results highlight the mitogenic role of the IR in mammary tumor growth with a direct link to CD24 expression.

Metastatic Type 1 Gastric Carcinoid – A Real Threat or Just a Myth?

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Aim: Metastatic GCA1 are extremely rare and there is no data about their natural history, treatment and prognosis. To describe disease characteristics and treatment modalities in a group of rare patients with metastatic gastric carcinoids type 1 (GCA1).

Methods: Information on clinical, biochemical, radiological, histopathological findings, the extent of the disease, as well as the use of different therapeutic modalities and the long-term outcome were recorded.

Results: We studied twenty consecutive patients with a mean age of 55.1 years. The mean follow-up period was 83 months. 12 patients had regional lymph node metastases and 8 patients had liver metastases. The mean primary tumor diameter was 20.13±10.83 mm (mean±SD). The mean Ki-67 index was 6.8%±11.2%. All but one patient underwent endoscopic or surgical excision. The disease was stable in all but 3 patients with progressive liver disease. All patients remained alive during the follow-up period.

Conclusions: Metastatic GCA1 carry a good overall prognosis. The metastatic potential appears to be related to a tumor size of ≥ 1cm, an elevated Ki-67 index and high serum gastrin levels. Endoscopic ultrasound is recommended in patients with these risk factors. Somatostatin analogues may be used, particularly in patients with multiple relapsing tumors, and with metastatic disease. Surgical procedures should be performed only in patients in whom total tumor excision is expected.

Bisphosphonates and the Risk of Breast Cancer in Osteoporotic Women: a Population-based Study

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Background: Bisphosphonates (BP) are widely used in osteoporosis treatment. By inhibiting the mevalonate pathway, bisphosphonates may affect cell function and survival, including the viability of tumor cells. Recently, a protective effect of bisphosphonates on breast cancer risk has been suggested by several studies, which were unable to exclude the possibility of a confounder effect due to low cumulative exposure to estrogen in osteoporotic women versus controls.

Study objective: To assess the association between different levels of bisphosphonate exposure and breast cancer incidence in a cohort of osteoporotic post-menopausal women.

Study methods: This historical prospective study was conducted using the computerized databases of Maccabi Healthcare Services (MHS). Included in the study were cancer-free women aged 55-75 who started bisphosphonate therapy between 1998-2012. Bisphosphonate exposure was expressed in quintiles of proportion of days covered with BP during follow-up period (PDC). Cancer incidence was ascertained by the Israel National Tumor Registry.

Results: A total of 16,628 eligible MHS members were identified and 275 cases of breast cancer diagnosed during a total follow-up period of 76 710 person-years. Compared to women with a PDC with bisphosphonates of 20% or lower, the hazard ratio for breast cancer were HR=0.89 (p=0.74)), HR=0.74 (p=0.38), HR=0.71(p=0.29) and HR=1.38 (p=0.21) among women with a PDC of 20-40%, 40-60%, 60%-80%, and 80% or higher respectively.

Conclusions: In the present study, we did not find any significant negative association between persistence with bisphosphonates and risk of breast cancer.

The Transcription Factor Nrf2 is involved in the Inhibition by Phytonutrients of IGF-I Activity in Cancer Cells and the Activition in Bone Cells

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Phytonutrient (polyphenols, carotenoid and their metabolites) were found to inhibit insulin-like growth factor I (IGF-I)-induced proliferation in cancer cells which is a beneficial effect. However, such inhibition is undesirable in bone where IGF-I is essential for bone health. Thus, we analyzed the effect of these phytonutrients on IGF-I activity in bone derived osteoblast-like cell. We used the human (MG-63) and mouse (MC3T3-E1) osteoblast like cells and MCF-7 breast cancer cells. IGF-I activity was assessed by measuring the proliferation of these cells (crystal violet) and the phosphorylation of AKT and AKT substrates (Western blot and ELISA). As expected, phytonutrients inhibited IGF-I-stimulated proliferation and AKT phosphorylation in breast cancer cells. In contrast, in the osteoblast cells these phytonutrients did not inhibit and even enhanced IGF-I activity. In order to examine the mechanism of the opposite effects of the phytonutrients in the two cell types, we examined the involvement of the Nrf2 transcription system which is activated by the phytonutrients. Our results suggest that Nrf2 is involved in these effects as its over-expression reduced the phosphorylation of AKT in cancer cells, and increased it in bone cells in a dose-dependent manner. Moreover Preliminary results with siNrf2 demonstrated that reduced expression of Nrf2 attenuate the inhibitory effect of phytonutrients on IGF-I activity in cancer cells.

In conclusion, we suggest that phytonutrients contribute to cancer prevention by inhibition of IGF-I activity and they enhance bone health by increasing the activity of the growth factor in osteoblasts. Activation of Nrf2 by the phytonutrients at least partially explains these opposite effects.

IGF1R tyrosine Kinase Inhibitor Enhances the Cytotoxic Effect of Methyl Jasmonate in Endometrial Cancer

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Methyl jasmonates (MJ) are plant stress hormones that exhibit anti-cancer activity and inhibit cancer cell growth. The insulin-like growth factor-1 receptor (IGF1R) is an emerging target for anti-cancer therapies. NVP-AEW541 belongs to the pyrrolo (2,3-d) pyrimidine class, with specific IGF1R tyrosine kinase inhibitory activity. NVP-AEW541 has been shown to abrogate IGF1-mediated IGF1R autophosphorylation and to decrease IGF1R signaling pathway activation. Given the potential overlap in the mechanisms of action and molecular targets of jasmonates and IGF1R inhibitors, and in view of the growing interest in the pharmacological applications of these compounds, the objectives of the present study were: (1) to assess the cytotoxic activity of MJ in Type I (endometrioid) and Type II (uterine serous carcinoma) endometrial cancer; and (2) to evaluate the hypothesis that the apoptotic and anti-proliferative actions of MJ can be enhanced by co-targeting the IGF1R signaling pathway. To this end, endometrial cancer cells were treated with MJ in combination with NVP-AEW541, and IGF1R and AKT phosphorylation, apoptosis and proliferation were measured. MJ, per se, had a potent pro-apoptotic effect and exhibited significant toxicity in all cell lines tested. Combined MJ and NVP-AEW541 treatment had significantly increased cytotoxicity. MJ did not affect IGF1R phosphorylation, however, it enhanced AKT phosphorylation and abolished the anti-apoptotic effect of IGF1. In summary, our findings suggest that combined selective IGF1R inhibitor and MJ treatment may constitute an attractive new modality for USC, a highly aggressive form of endometrial cancer.

Involvement of Reactive Oxygen Species and microRNAs on Hypoxic Responses in Granulosa Cells

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Hypoxia-inducible factor-1α (HIF-1α) is an important transcription factors in the angiogenic process that accompanies corpus luteum formation. Using human granulosa cell (GC) line as a model, we investigated the involvement of Reactive Oxygen Species (ROS) and micro RNAs (miRs) in HIF-1α regulation and the subsequent effects on VEGF and endothelin-2 (EDN-2). We observed that ROS alone is sufficient to induce HIF-1α protein in cells, as H2O2 elevated the levels of HIF-1α protein as well as EDN-2 and VEGF gene expression in normoxia. In cell cultured with CoCl2, hypoxia mimetic, a broad-range scavenger of ROS ablated the increase in HIF-1α protein and HIF-1α induced genes.

Besides ROS, miRNAs are ideal mediators of hypoxic stress responses as they are able to modify gene expression rapidly and reversibly. Among them, miR-210 is a direct transcriptional target of HIF-1α. We found that along with HIF-1α accumulation, CoCl2 dose dependently elevated miR-210 production in GCs. HIF-1α knockdown using specific siRNA (90% less than in scrambled siRNA) abolished the induction of miR-210 under hypoxic conditions demonstrating its dependency in HIF-1α. Interestingly, miR-210 over-expression promoted the induction of VEGF and EDN-2 mRNAs under hypoxic and normoxic conditions. A similar, but mirror-image response was observed with miR-210 inhibition; anti-miR-210 reduced EDN-2 and VEGF without decreasing HIF-1α protein levels in normoxia. ROS and miR-210 constitute novel regulators of VEGF and EDN-2 in ovarian granulosa cells; they may operate in HIF-1α dependent and independent manner.

These provide new perspective in our understanding of processes that constitute hypoxic tissue development.

Effects of Hyperglycemia on Reproduction through Altering the Gonadotrope Epigenome

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Metabolic state affects reproduction by altering synthesis and release of the gonadotropin-releasing hormone (GnRH) from the hypothalamus. However the pituitary gonadotropes do not become insulin-resistant in states of hyperglycemia, suggesting that high circulating levels of glucose could affect reproduction also via direct actions on the pituitary. We hypothesized that in states of chronic hyperglycemia, entry of elevated glucose into the gonadotropes results in a reduction in the activity of Sirtuin histone deacetylases (Class III HDACs) that require NAD+ whose levels drop during states of high glucose metabolism. This would lead to aberrant histone hyperacetylation and consequent changes in gene expression and likely also gonadotrope dysfunction. To test this, αT3-1 gonadotrope-precursor cells were exposed to high glucose (HG) for 4-32 days and the effects on a glucose-sensitive reporter gene were measured. Levels of this reporter gene increased after 4 days HG, and remained high during the entire experiment. We observed an increase in acetylation of lysines on histones H3 and H4 following incubation of the cells in HG, and similarly after their exposure to the Sirtuin inhibitor, Nicotinamide. The expression of two Sirtuin enzymes which reportedly self-regulate was reduced by the HG, and several key genes in gonadotrope function were also affected, albeit to a lesser degree. Notably, however GnRHR mRNA levels appeared elevated. Our results suggest that a state of chronic hyperglycemia may repress Sirtuin activity to alter gonadotrope function, with likely aberrant gene expression and/or responsiveness to GnRH.

"An ounce of prevention is worth a pound of cure" - GnRH-agonist cotreatment in parallel to chemotherapy increases pregnancy rate.

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The late effects of cancer treatment have gained a worldwide interest. We have administered monthly GnRH-agonistic analogue to more than 250 young women exposed to gonadotoxic chemotherapy. These patients were compared to a control group of over 130 patients of comparative age (14-40 years), who were similarly treated with chemotherapy without GnRH-a. Results: Less than 11% developed irreversible hypergonadotropic amenorrhea in the GnRHa cotreatment group, vs 51% in controls [P0.05]. The remaining patients resumed cyclic ovarian function, and 56 patients spontaneously conceived 85 times, and were delivered of 71 healthy neonates, in the GnRHa group. In the control group only 28 pregnancies were reported in 18 patients [P0.05]. One patient, in the GnRHa group, spontaneously conceived three times and was delivered of three healthy neonates despite two stem cell transplantations [SCT], 11 years apart. Another patient spontaneously conceived four times and was successfully delivered of four healthy children. GnRH-a cotreatment was beneficial not only against regular chemotherapy but also for lymphoma patients undergoing SCT. Most relevant to this equivocal and highly debatable issue, is a recent publication from one of the previous opponents to GnRH-a use for fertility preservation, reporting that the use of GnRH-a during chemotherapy has also significantly increased the probability to become pregnant. Conclusions: GnRHa cotreatment in parallel to chemotherapy may increase pregnancy rate in survivors. Therefore, it should be offered to every young woman before gonadotoxic chemotherapy in addition to cryopreservation of embryos, ova, and ovarian tissue.

The Role of Hyaluronic Acid in Embryo Implantation

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Implantation is a critical step in the establishment of pregnancy, during which the embryo attaches to and invades the maternal uterus. One of the characteristics of early pregnancy is a marked increase in the permeability and density of the uterine blood vessels that allow the delivery of oxygen and nutrients to the embryo until the placenta becomes functional. Hyaluronic acid (HA) was reported to participate in the regulation of vascular development. Specifically, high-molecular-weight HA has been shown to inhibit angiogenesis during development, whereas its enzymatic degradation products are pro-angiogenic. Interestingly, significant changes in HA distribution in the endometrium were observed during implantation, suggesting a potential role of this molecule in endometrial stroma preparation for embryo implantation. Preliminary results, generated by functional MRI inspection of live pregnant mice (E6.5) treated with HA synthesis inhibitor 6-diazo-5-oxo-1-norleucine (DON), showed a marked increase in decidual blood vessel permeability and accumulation of blood in close proximity to the implanted embryo. Moreover, significant changes in the gene expression profile of HA synthesizing and degrading enzymes, and its ECM stabilizing proteins, were observed in the implantation site during early pregnancy. These observations made us raise the hypothesis that HA metabolism participates in the regulation of uterine angiogenesis in early pregnancy. In this study we will investigate the regulatory effects of HA on vascular development and remodeling during embryo implantation in mice. Our results will potentially shed light on the physiological processes leading to unsuccessful implantation resulting in pregnancy failure.

Gonadal Dysgenesis as an Unusual Presenting Symptom of Frasier Syndrome

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Background: Frasier syndrome (FS) is characterized by deteriorating proteinuria in childhood, that preceeds the presentation of gonadal dysgenesis. Glomerular podocyte and gonadal development is probably sensitive to underrepresentation of WT1-KTS+ isoforms that is caused by mutations in the donor splice site in intron 9 of WT1 gene. We present an unusual case of FS presenting initially with severe XY gonadal dysgenesis.

Clinical Data: A 18-year-old phenotypic female presented with delayed puberty (Tanner-III), and primary amenorrhea. Hormonal studies exemplified hypergonadotropic hypogonadism; karyotype was XY. Imaging studies revealed a normal uterus and fallopian tubes, but streak gonads. Only at 19y of age, she presented with nephrotic syndrome with no prior evidence of proteinuria or growth failure.

Molecular data: Sequencing of leukocyte DNA for SRY and SF-1 was normal while in WT1-gene a de-novo mutation IVS9+5G□A in intron-9 was detected; confirming the diagnosis of FS. Following Prophylactic gonadectomy, histolopathology revealed epididymal & ovarian tissues with no germ cells in Lt gonad, and streak Rt gonad. Further cDNA studies are underway to elucidate whether the WT-1 downstream transcription factors (SRY, SF-1) are present in these gonads.

Conclusions: Gonadal dysgenesis may preceed the clinical presentation of glomerulopathy in FS. Sequential kidney function and urine protein testing are indicated and may prevent irreversible damage in cases of gonadal dysgenesis. Presence of SRY and SF-1 transcripts in the removed gonads may elucidate the interrelations between WT-1 and other major transcription factors in early gonadal development.

Reciprocal Inhibition between Thrombospondins and FGF2 is Key to Luteolysis

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The luteolytic hormone, prostaglandin F2α (PGF2α) regulates angiogenesis-modulating factors in a luteal stage-dependent way. FGF2, a potent pro-angiogenic factor in the CL was markedly increased in the PGF2α-refractory Day4 corpus luteum (CL). In contrast anti-angiogenic factors, thrombospondin-1 and 2 (TSP-1; TSP-2) and their CD36 receptor, were upregulated by PGF2α specifically in Day11 CL undergoing luteolysis. We have also previously shown that FGF2 dose-dependently enhanced luteal endothelial cells (EC) migration and proliferation. Here we further investigated the effects of TSPs in luteal cells and their relevance to luteolysis, TSP-1 was the dominant form in EC, and TSP-2 in granulosa cells (GC). CD47 did not exhibit preferential expression between EC and GC, while CD36 was confined to GC. Accordingly, mimetic peptide of TSP-1 sequence that binds CD36 receptor (ABT-898) reduced only GCs numbers. TSP-1 and 2 were dramatically induced in vitro by PGF2α in GC. Conversely, luteinization by LH with and without insulin decreased expression of TSP-1, 2 and CD36. Importantly, this treatment increased FGF2 expression in GC suggesting a reciprocal inhibition between TSP-1 and FGF2. Indeed, addition of FGF2 inhibited TSP-1 mRNA and vice versa, TSP-1 treatment decreased FGF2 expression. In agreement, ablation of TSP-1 with specific siRNA elevated FGF2 mRNA and protein levels. Furthermore, in TSP-1-silenced EC, phosphorylation of MAP kinase was increased compared with cells transfected with scrambled siRNA. These observations demonstrate interplay between TSP-1 and FGF2 in various ovarian cells and suggest that the inhibition of FGF2 expression and activity by TSP-1 is decisive for luteal regression.

Personalized Medicine for Diabetes and its Complications: The Future is Now

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Diabetes is a complex and heterogeneous disease in which the genomic architecture spans from uncommon single gene (monogenic) forms to more common polygenic forms in which lifestyle and other factors play pivotal roles. There are more than 40 different monogenic forms of diabetes constituting approximately 3 to 5% of all diabetes cases. Identification of these genes has unveiled new biological insights into glucose homeostasis and the pathophysiological basis of diabetes. Despite this new knowledge, the vast majority of monogenic diabetes cases go undiagnosed resulting in suboptimal treatment and missed opportunities for family-based screening for early diagnosis and/or prevention. Clinical prowess and targeted molecular testing can now be employed to diagnose monogenic forms of diabetes. Furthermore, genetic variants have been identified that can predict drug response for medications commonly prescribed for diabetes and its cardiometabolic complications. This case-based Meet-the-Professor session will provide an overview of how today's knowledge of genomics can be applied to improve diagnosis and treatment for diabetes and its complications.

Hypoparathyroidism

Sophia Ish Shalom

Hypoparathyroidism - Diagnostic and Theraputic Dilemmas
Technion- The Israeli Institute of Technology

Natural History of TSH Receptor (TSHR) Mutations: Insights from Long-term Fllow-up of 94 Affected Children

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Loss-of-function mutations in the TSH receptor (TSHR) lead to resistance to TSH (RTSH) syndrome presenting with either congenital hypothyroidism (CH) or subclinical hypothyroidism (SCH). Despite several reports of patients affected with TSHR mutations, data on the long-term outcome of this condition are limited. The aim of the present study was to assess the prevalence of TSHR mutations among children with RTSH characteristics and to evaluate the outcome of this condition over time. The TSHR was sequenced in 94 subjects (ages 3 days -21 years) with non-autoimmune SCH or with CH with RTSH characteristics. Clinical and hormonal parameters were collected from the medical files. Twenty-seven subjects (29%) carried mutations in TSHR. Six different mutations were identified: c.484CG (p.P162A); c.202CT (p.P68S); c.790CT (p.P264S); c.269AC (p.Q90P); c.1957CG (p.L653V); c.1348CT (p.R450C). Twelve subjects were homozygous, three were compound heterozygous and twelve were heterozygous. Twelve sequence variants have been found. Homozygous patients had a more severe phenotype (TSH; 29.0 vs. 14.2, p = 0.002). Patients were followed for as long as 11 years. Mean serum TSH and FT4 levels at presentation and at last visit did not differ significantly. Heterozygous patients had only mild hyperthyrotropinemia with stable TSH levels and did not required replacement therapy. Homozygous subjects tend to increase TSH and decrease FT4 with time and replacement therapy was initiated in 11 subjects based on clinical judgments. SCH in heterozygous carriers is a stable compensated condition with an appropriately adjusted set point of pituitary–thyroid feedback that does not require replacement therapy. Homozygous subjects may develop uncompensated SCH over time that could necessitate L-T4 therapy. Replacement therapy should be considered on an individual basis and long-term follow-up is recommended.

Mineralo and Glucocorticoid Deficiency in Early Infancy are Caused by a Novel Mutation in the Nicotinamide Nucleotide Transhydrogenase Gene

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Background: NNT (Nicotinamide Nucleotide Transhydrogenase) gene mutation has been recently shown to cause familial glucocorticoid deficiency (FGD), probably by decreasing reactive oxygen species detoxification in adrenocortical cells. Affected infants typically present within the first few months with isolated glucocorticoid deficiency. We report a novel NNT gene mutation, in two Palestinian kindreds presenting uniquely with neonatal addisonian crisis (both mineralo and glucocorticoid deficiency) in 4 cases.

Clinical data: Family A: Palestinian male infant with normal external genitalia born to consanguineous parents, presented neonatally with Na: 118, K:6 mmol/l, decreased basal and ACTH stimulated Cortisol and 17-hydroxyprogesterone, normal infantile Testosterone, and elevated Plasma Renin Activity(15ng/ml/hr). Two female cousins had similar manifestations. Family B: female neonate from consanguineous kindred presented with similar phenotype.

Results: Whole exom sequencing in two affected cousins from family A revealed G200S homozygous mutation in NNT gene. The variant segregated with the disease in the family, and all three pairs of parents were heterozygous. In family B the affected patient was homozygous G200S and parents were heterozygotes. Haplotype analysis and expression studies studying the ROS detoxification capacity in fibroblasts are underway.

Conclusion: The novel G200S mutation in the very recently described NNT gene causes uniquely early-infantile-addisonian crisis with both mineralo and glucocorticoid deficiency. NNT mutations should be added to the differential diagnosis of addissonian crisis. Given the ubiquitous nature of NNT, further studies of various mutations are required to elucidate the specific target organs prone to develop pathologies in relation to their impaired antioxidant defense.

Glucocorticoid Regimens for Prevention of Radioiodine-Associated Exacerbation of Graves' Orbitopathy – Systematic Review and Meta-Analysis

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Background: Progression of Graves' orbitopathy (GO) after radioactive iodine therapy (RAI) for Graves' hyperthyroidism is a well-documented phenomenon. While glucocorticoid therapy has been shown to prevent this progression, there is wide variation in the type, route and duration of glucocorticoid regimen used.

Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) and non-randomized controlled trials comparing glucocorticoid regimens versus placebo, no intervention, or other glucocorticoid regimens.

Results: Eight trials evaluating 850 patients fulfilled inclusion criteria. In patients with preexisting GO, oral prednisone (0.4-0.5mg/kg, 25-40mg/d) was very effective in preventing GO progression (RR 0.11. 95%CI 0.04-0.3, 4 studies), while in patients without known GO there was a non-statistically significant trend in favor of treatment (RR 0.16, 95%CI 0.02-1.13). Treatment duration was ≥3 months in 3 RCTS, and 1-2 months in two retrospective studies. Low dose prednisone (mean 0.22mg/kg) given for 6 weeks was effective in patients with minimal or no GO in one retrospective study. Intravenous methylprednisolone was evaluated in 9 patients, of which none had new onset GO. Oral betamethasone was evaluated in 2 RCTs and was ineffective. Glucocorticoid treatment did not affect the efficacy of RAI for hyperthyroidism (RR 1.05, 95%CI 0.69-1.58).

Conclusions: Current evidence supports the use of oral prednisone 0.4-0.5mg/kg for prevention of RAI associated GO progression in patients with preexisting GO, tapered over 3 months. Low dose prednisone given for 6 weeks showed promising results in patients with minimal or no preexisting GO, but further studies are needed. In patients without preexisting GO, data is insufficient to recommend routine glucocorticoid preventive treatment.

Anti Thyroid Antibodies, Parietal Cell Antibodies and Anti Tissue Transglutaminase Antibodies in Patients with Autoimmune Thyroid Disease

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The co-existence of several tissue-specific autoantibodies in autoimmune thyroid disease (ATD) is well established. The published prevalence of positive anti parietal cell antibodies (APC- Ab) is 20-25% and that of celiac antibodies is 2-5%.

The aim of our study was to determine the prevalence of APC-Ab and anti-tissue transglutaminase- IgA antibodies (tTG-Ab) in endocrinology clinic patients with ATD. **Methods:** 120 consecutive patients with ATD were evaluated for anti-thyroglobulin antibodies (TG-Ab), anti-thyroid peroxidase antibodies (TPO-Ab), APC-Ab and tTG-Ab. Patients with positive APC-Ab and/or tTG-Ab were referred for upper GI endoscopy. Gastrin levels were assessed in patients with positive APC-Ab.

Results: Twelve males (10%) and 108 females (90%) were evaluated. 20% were Arabs and 93.33% had Hashimoto's thyroiditis.

Thirty five (29.16%) subjects had positive APC-Ab. This rate was similar in different **subgroups:** Jews versus Arabs (30.2% vs. 25%, respectively); Hashimoto's thyroiditis versus Graves' disease (29.4% vs. 25%); males versus females (33.3% vs. 28.7%). Twenty three of the APC-Ab positive subjects underwent an upper GI endoscopy. Gastritis was documented in 22 (95.65%).

Mean gastrin level in this subgroup was 688.68 pg/ml.

Five of 114 tTG-Ab tests were positive (4.38%). All were females with Hashimoto's thyroiditis. Rates were equal in Jews and Arabs. One 61 years old female had both PC-Ab and tTG- Ab positive.

Conclusions: Considering the frequency of APC-Ab and tTG-Ab positivity in ATD, checking for the presence of these two entities should be an integral parcel of the workup of this disease.

Use of the Bethesda System for Reporting Thyroid Cytopathology Improves the Detection of Malignancy in Indeterminate Nodules

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Introduction: The new Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was developed in 2009 to standardize the terminology for thyroid FNA results. Objective: To investigate the impact of TBSRTC on the number of indeterminate nodules excised and its correlation with the final pathologic diagnosis. Methods: All thyroid FNAs performed at Rabin Medical Center in 2011-2012 were revised. The clinical and pathologic data on Bethesda 3 and 4 nodules were collected from the electronic records. Results were compared to our published data from 1999-2000. Results: Of the 3794 nodules aspirated at our center during the study period (twice the number than in 1999-2000), 552 (14.5%) were categorized as B3-B4. Medical records were available for 322 (58.3%). Thyroidectomy was performed in 122/322 cases (38%): 65/250 (26%) B3, 57/72 (79%) B4. Differentiated thyroid cancer was found in 66/122 (54%): 30/65 (46%) of B3, 36/57 (63%) of B4, with a trend-level difference between groups (p=0.089). Comparison of patients operated/not operated for B3 disease yielded no differences in age and sex, but the non-operated group had more benign repeated cytologic results (63% vs 30%, p0.001) and smaller nodules (22.2±10 vs 27.2±13 mm, p=0.014). Compared to 1999-2000, while the number of FNAs of indeterminate nodules increased from 6% (111/1854) to 14.5%, the surgery rate decreased from 55% (58/111) to 38%, and the diagnostic accuracy of malignancy increased from 26% (15/58) to 54%. **Conclusions:** Application of the Bethesda system significantly improves diagnostic accuracy for indeterminate thyroid nodules, leading to higher malignancy detection despite lower thyroidectomy rates.

Vitamin D and the Estrogen Receptor β Agonist cDtboc Synergistically Affect Thyroid Cancer Cell Growth

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Background: Estrogen Receptors (ERs), Vitamin D Receptors (VDR) and 1α -hydroxylase 25- hydroxy vitamin D (1OHase) are expressed in various normal and cancer cells.

Aims: To assess whether vitamin D metabolites (VDMs) 1,25D, 24,25D and 25D modulate the mRNA expression of ERs, 1OHase, VDR and cell proliferation (CP) in Papillary Thyroid Carcinoma (PTC) cells.

Methods: ERα, ERβ, VDR, 1OHase expression and CP were determined by rtPCR and by direct measurement in 7 PTC tissue and normal thyroid tissue from the same patients.

Results: ERα, VDR and 1OHase mRNA was more abundantly expressed in normal than cancer cells, whereas ERβ mRNA expression was similar in both cell types. In cancer cells VDMs increased mRNA expression of ERα, ERβ and VDR, but not of 1OHase, whereas in normal cells VDMs elicited an increase in the mRNA expression of all genes of interest, with the exception of ERβ. VDM dose dependently inhibited CP in both cell types, but the effect of 1,25D was more potent in cancer cells. The ERβ mimetic agent Carboxy-Daidzein-tboc (cDtboc) also inhibited CP in a dose-related fashion, and cancer cells were more sensitive than normal cells to this inhibitory action. Combined treatment of VDMs and low concentration of cDtboc inhibited CP only in cancer cells.

Conclusions: VDMs alone and in conjunction with cDtboc differentially exert an inhibitory effect on CP in PTC. This finding might form the basis for the use of hormonal therapy in human thyroid cancer.

ERK Phosphorylates FAK and Paxillin in GnRH-stimulated Signalosome: Possible Role in Gonadotropes Migration

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We have recently described a preformed multi protein complex (signalosome) associated with the GnRH receptor (GnRHR) in pituitary gonadotrope cells. This signalosome included c Src, focal adhesion kinase (FAK), paxillin, vinculin, tubulin, caveolin-1, protein kinase C (PKC) δ, PKCε, PKCα, Ras, kinase suppressor of Ras-1 (KSR), MAPK kinase (MEK) 1/2, ERK1/2 and the GnRHR. Incubation of LβT2 gonadotrope cells with GnRH resulted in a rapid phosphorylation of caveolin-1, FAK, vinculin, and paxillin on Tyr residues by the GnRH-activated c-Src. Then, GnRH activated ERK1/2 in the complex in a c-Src-dependent manner, and the activated ERK1/2 subsequently phosphorylated FAK and paxillin. Addition of GnRH to LβT2 cells transfected with GnRHR-mCherry and ERK-GFP resulted in bleb formation, ERK accumulation in the blebs and apparent cell migration. Also, addition of GnRH to LβT2 gonadotrope cells transfected with GnRHR-mCherry and paxillin-GFP resulted in enrichment of paxillin in focal adhesions in the newly formed blebs. Moreover, caveolin-1 and vinculin, which are members of the signalosome, accumulated in the blebs. Treatment whit U0126, a MEK inhibitor, caused a decreased in bleb formation. Addition of EGF to LβT2 cell resulted in minimal bleb formation, suggesting that the bleb formation is mediated via the GnRHR. We therefore propose that the role of the signalosome is to sequester a cytosolic pool of activated ERK1/2 to phosphorylate FAK and paxillin at focal adhesions apparently to mediate gonadotropes migration.

The CYP2E1-NRF2 Pathway: Negative Regulator of Insulin Responsiveness and Energy Balance

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Imbalanced equilibrium between energy intake and expenditure results in obesity and is associated with oxidative stress. CYP2E1, working partly via NRF2 transcription factor, induces oxidative stress leading to insulin resistance. We showed that CYP2E1 knockout mice were protected against high-fat diet (HDF)-induced insulin resistance and obesity and had higher energy expenditure.

As impaired function/expression of GLUT4 in insulin target tissues characterizes insulin resistance, we studied whether CYP2E1 and NRF2 regulate GLUT4 gene in primary rat adipocytes and skeletal muscle-derived L6 cells. CYP2E1 impaired insulin-stimulated translocation and function of GLUT4 in a ROS-dependent manner while its silencing had the opposite effects. CYP2E1 and NRF2 overexpression suppressed GLUT4 expression while their silencing had the opposite effect. CYP2E1-induced suppression of GLUT4 was mediated by NRF2, as it was reversed by a co-expressed dominant-negative, but not wildtype, NRF2. Promoter-reporter, subcellular distribution and chromatin immunoprecipitation analyses revealed that CYP2E1 suppressed GLUT4 via enhancing the nuclear localization and the subsequent binding of NRF2 to GLUT4 promoter 58-326 bp region that includes NRF2 binding motifs.

Energy expenditure is mainly regulated by the brain. Indeed, using immunohistochemical staining we found that CYP2E1 and NRF2 protein levels were higher in hypothalamus, cerebellum and cortex of HFD-fed, compared to CHOW-fed mice.

Our findings introduce the CYP2E1-NRF2 pathway as negative regulator of insulin responsiveness and energy balance. While hypothalamic nuclei are known to regulate energy expenditure, the role CYP2E1/NRF2 induction in other brain areas needs to be deciphered.

Regulation of Tet1 and Tet2 Expression in the Gonadotrope by Gonadotropin-Releasing Hormone

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DNA methylation (5-methylcytosine; 5mC) is an epigenetic mark that plays a crucial role in development and gene regulation. Mechanisms of DNA demethylation are not fully understood, but the Tet family of deoxygenases that catalyze the oxidation of 5mC to 5-hydroxymethylcytosine are likely involved. We have found that in αT3-1 gonadotrope-precursor cells, expression of Tet1 and Tet2 is altered by GnRH, leading to a decrease in Tet1 and an increase in Tet2 mRNA levels. In order to elucidate the pathways involved, we treated αT3-1 and/or LβT2 cells with PMA to activate the protein kinase C (PKC) pathway, the calcium ionophore ionomycin, or forskolin to activate the cAMP/protein kinase A (PKA) pathway. PMA had no effect on Tet1 mRNA levels, but did increase those of Tet2, while ionomycin decreased levels of both transcripts, with a stronger effect on Tet1. In contrast, forskolin repressed Tet1 and activated Tet2 expression. Confirmation of the role of the cAMP/PKA pathway in mediating the distinct GnRH effects on each of the Tet genes, was seen by pre-incubation of cells with the PKA inhibitor, H89 which abolished both the GnRH inhibitory effect on Tet1 and its stimulatory effect on Tet2. Our results suggest that the divergent effects of GnRH on expression of the Tet enzymes are mainly through the cAMP/PKA pathway, although PKC activation may also increase Tet2 transcription. We have thus shown a regulatory role for GnRH on expression of these enzymes which likely helps shape gonadotrope function, and have begun to elucidate the intracellular mechanisms involved.

Plant Polyphenols Inhibit Cellular 24-Hydroxylase (CYP24A1) Expression and Elevate Serum 25-Hydroxyvitamin D Levels

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1α,25-dihydroxyvitamin D_3 (1,25D) is known to regulate various cellular functions, including proliferation and differentiation. Both 1,25D and its precursor, 25-hydroxyvitamin D_3 [25(OH)D], are catabolized by 24-hydroxylase encoded by CYP24A1, which is the most responsive vitamin D target gene and a is candidate oncogene frequently overexpressed in malignancies. Therefore, compounds which can inhibit CYP24A1 expression and/or activity, thereby reducing degradation of vitamin D derivatives, may potentiate their anticancer effects. We have previously shown that the plant polyphenols carnosic acid, curcumin and silibinin synergistically enhance differentiation of acute myeloid leukemia (AML) cells induced by near physiologic concentrations of 1,25D. This was associated with elevation of the vitamin D receptor (VDR) and retinoid X receptor alpha (RXRα) protein levels. Here, we demonstrate that despite promoting functional upregulation of VDR/RXRα, these polyphenols markedly inhibited 1,25D-induced CYP24A1 mRNA expression in AML cell lines but not in osteoblastic cells. Furthermore, while potentiating 1,25D-induced transactivation of the vitamin D responsive element (VDRE), the polyphenols strongly inhibited 1,25D-induced activation of CYP24A1 promoter activity. Importantly, feeding of healthy Balb/c mice with standard rodent chow supplemented with carnosic acid-rich rosemary extract resulted in a dose- and time-dependent increase in serum levels of 25(OH)D, as compared to control animals. Collectively, the above data suggest that by downregulating CYP24A1 in a tissue-dependent manner, plant polyphenols may potentiate therapeutic and preventive effects of vitamin D derivatives. These findings may also contribute to our understanding of the beneficial effects of healthy diets. (Supported by the Israel Science Foundation grant 635/11 to MD and YS).

The Correlation between 25 Hydroxyvitamin D, Parathyroid Sestamibi Scan and Size of Parathyroid Adenoma in Patients with Primary Hyperparathyroidism

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Introduction: Vitamin D deficiency is common in patients with primary hyperparathyroidism (PHPT). Co-existence of vitamin D deficiency and primary hyperparathyroidism may complicate PHPT due to its deleterious effect on bone. The size of parathyroid adenomas in some studies was found to be greater in patients with vitamin Ddeficiency but whether these adenomas are more easily found during imaging studies is not clear.

Objective: to determine the relationship between the levels of 25OH vitamin d (25[OH]D) ,parathyroid sestamibi scan (MIBI) and the size of parathyroid adenoma in patients with primary hyperparathyroidism

Design: Retrospective analysis of patients referred for a parathyroid sestamibi scan because of primary hyperparathyroidism. Data from the charts included demographics, laboratory data results of MIBI scan ultrasound and pathology report.

Results: A total of 411 charts were reviewed, data could be extracted from 299. The mean age was 61.4 (±14.4), 57 (13%) men and 242 (81%) women. The calcium level was 10.9 mg/dl (± 0.5), vitamin D 44.6 nmol/L (± 23.4) and PTH 128.4 pg/ml (± 80.7). Vitamin D level was similar in patients with a positive and a negative MIBI scan (44.5 nmol/L ± 23.6 and 45.4 nmol/L ± 22.7, respectively). The weight of the adenoma was not significantly higher in patients with lower levels of vitamin D. The mean adenoma weight was not different in patients with a positive or a negative MIBI scan.

Conclusion: Lower vitamin D levels were not related to larger parathyroid adenomas or to a higher rate of positive MIBI scans.

Ketoconazole Enhances in vitro the Inhibitory Effect of Vitamin D Analog in Combined Treatments of Lung Cancer Cells

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Background: 1.25(OH)2D3, is a well-known anticancer agent. However, its clinical use is restricted because of hyper-calcemic effects. To overcome this drawback, low-calcemic analogs were synthesized. However, efficacy of vitamin D agents is blunted due to catabolism by 24-hydroxylase, a member of the cytochrome P450 super-family. Ketoconazole is an inhibitor of these enzymes. Another obstacle is the decreased vitamin D receptor-mediated transcriptional activity induced by transcriptional co-repressors, comprising histone deacetylases (HDAC). Sodium valproate (VPA) inhibits HDAC. Its addition to 1.25(OH)2D3 enhances the DNA-damaging effect of radiation (Gavrilov et al., 2010). Combinations of the vitamin D analog calcipotriol, the 24-hydroxylase inhibitor ketoconazole and the HDAC inhibitor VPA with the DNA-damaging drug cisplatin, were used in the present study in order to restrain growth of non-small cell lung cancer cell line A549.

Aim: To evaluate the effect of ketoconazole on vitamin D degradation and to assess A549 cell growth inhibition by 1.25(OH)2D3/ketoconazole combination, and by four-drug combination of calcipotriol/ketoconazole/VPA/cisplatin

Methods: The effects of the treatments on 1.25(OH)2D3 catabolism, cell growth and cell-cycle were assessed. Combined effects were determined by 48h pre-treatment with calcipotriol/ ketoconazole/VPA followed by additional 72h incubation with cisplatin.

Results: Ketoconazole inhibited 1.25(OH)2D3 catabolism. The four-drug combination was the most efficient and suppressed A549 cell growth by 71.3%. This was supported by the cell-cycle experiments showing an arrest in S and G2-M phases and enhanced apoptosis.

Conclusions: The results emphasize the role of ketoconazole alone and in combination with other drugs in preventing vitamin D degradation and consequently maintaining its unimpaired anti-carcinogenic activity.

Is the Android Fat Deposition Induced by Higher Circulating Serum Free Cortisol in Men vs. Women?

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Objective: The effect of gender on the hypothalamic-pituitary-adrenal axis (HPA) has not received much attention. Only recently several studies have emerged pointing to the fact that women exhibit lower hair cortisol than men. Accordingly our aim was to elucidate the gender differences in serum free cortisol in the basal and ACTH-stimulated state.

Methods: Low-dose 1-µg ACTH test was performed in 85 subjects, 61 female, 24 males. Serum total cortisol (TC) was determined by an ECL method, and serum free cortisol (FC) was measured by the same method following equilibrium dialysis.

Results: Basal TC levels and post-ACTH stimulation did not differ between males and females. In contrast, basal serum FC levels in women was ~65% higher in men than in women (0.52±0.32, 0.86±0.62, ug/dl P=0.0017, adjusted for age). The FC fraction (% free cortisol, out of total cortisol) was concordantly higher in men (6.2 ±3.9% vs. 4.1 ±2.5%; p0.04)). Likewise, peak ACTH- stimulated FC levels were significantly higher in men compared to women (1.87±0.76, 1.43±0.8, ug/dl P=0.025) as was the area under the response curve, (73.6±25.3 vs. 52±25.3 ug Xmin; P=0.004).

Conclusion: Gender is a formerly unknown determinant of serum free cortisol in humans. This may be related to the well-known up regulation of cortisol binding globulin by estradiol, leaving less cortisol in the free circulating pool. Since cortisol tends to induce central fat deposition, we speculate that higher circulating free cortisol in men may contribute to gender-related fat distribution (android vs. gynecoid). Studies are underway to test these hypotheses.

High Prolactin Levels in Transsexual Women are Related to the Anti-androgen Treatment Modality

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Background: Treatment of male to female transsexual individuals consists of a combination of estrogen and anti-androgenic compounds including cyproterone acetate (CA), spironolactone, and GnRH analogues (GA). Modest hyperprolactinemia is almost universal in series using a combination of ethynil-estradiol and CA. These high prolactin levels have been attributed to estrogen being administered in supra-physiological doses.

Aims: To characterize the frequency and causes of hyperprolactinemia during hormonal treatment of transsexual women.

Methods: Retrospective study of patients treated in the transgender clinic of a tertiary referral center.

Results: 129 transsexual women (mean age 28.4 ± 10.26 years) treated in our clinic were followed for a mean period of 17.5 ± 21.5 months).

Smokers and patients with co-morbidities were preferentially treated with transdermal estrogen and GA (n=11, 10%) whereas oral β- estradiol and CA (n=75, %68) or spironolactone (n=19, 17.3%) were used in others. Estrogen treatment was titrated to achieve estradiol levels in the normal pre-menopausal range.

A significantly greater increase in prolactin levels (mIU/l) over baseline was already evident 3 months after initiation of CA treatment (392±333) in comparison to spironolactone (9.8±89) and GA (64±268) treated patients, p=0.0002), reaching peak levels of 828±109, 359.6±66 and 307±78 mIU/l respectively (p0.001).There was no correlation between prolactin and estradiol serum concentrations.

Conclusions: CA treatment was associated with a pronounced increase in prolactin levels, in comparison to other anti-androgenic therapies, independent of estradiol levels. Our results shed a new light on the pathophysiology of hyperprolactinemia during cross-sex hormonal treatment of transsexual women, with possible clinical implications.

Mutated SYCE1 Causes Autosomal Recessive Primary Ovarian Failure

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Context: Primary ovarian insufficiency (POI), results from ovarian follicle depletion with a consequent phenotypic spectrum ranging from absence of pubertal maturation to early menopause. Genes involved in essential steps in chromosome synapsis and recombination during meiosis, such as synaptonemal complex central element 1 (SYCE1), has been shown to cause POI in animal model. We describe for the first time a homozygous mutation in the SYCE1 in humans.

Objective: To identify the genetic cause of POI in an Israeli Arab family with consanguineous pedigree.

Design and Setting: A family-based genetic study, conducted at a tertiary care medical center.

Patients: Five family members were genotyped, including, two affected sisters, their consanguineous parents and their unaffected sister.

Intervention: The DNA from the five family members was subjected to whole-exome sequencing. The genotypes of interest were confirmed by Sanger sequencing and were further genotyped in additional 90 ethnically matched control individuals.

Results: A nonsense homozygous mutation (c.613CT) in SYCE1 gene was identified in the two affected sisters. The parents were heterzoygotes and the unaffected sister did not carry the mutation. The mutation was not identified in a DNA sample of 90 controls.

Conclusion: Due to the known SYCE1 gene function we suggest that nonsense mutation in that gene is responsible for the POI phenotype. These results highlight the importance of synaptonemal complex and meiosis in ovarian function.

Monitoring GnRHa Treatment in Girls with Central Precocious Puberty: A Comparison of Four Methods

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Objective: The gold standard for effective hormonal suppression in GnRHa-treated girls with precocious puberty (PP) is attenuated LH response to GnRH stimulation. We aimed to compare basal and post-GnRHa LH levels to GnRH stimulation test, and to evaluate first-voided urinary LH (ULH) as a non-invasive alternative for monitoring treatment. Methods: Seventeen girls with PP were followed over a period of 12 to 36 months during GnRHa treatment. ULH and serum LH levels were obtained before and 24 hr after GnRHa administration respectively every 4 months, along with clinical evaluation of puberty, growth and bone-age progression. GnRH stimulation test was performed 4 months after the first injection and annually thereafter. Pre-pubertal cutoff for ULH was 1.62 IU/L (2SD above mean ULH in 29 prepubertal girls).

Results: A total of 36 LHRH stimulation tests demonstrated adequate suppression of gonadotropins (peak LH 0.57±0.33; range 0.1-1.4 IU/L). Corresponding basal and post-GnRHa LH levels were 0.27±0.16 and 0.59±0.33 IU/L respectively and both tests were highly correlated with stimulated LH: R=0.956 and R=0.957 respectively. Corresponding ULH levels were 1.12±0.38 IU/L. Among 90 pair-tests of ULH and post-GnRHa LH measurements obtained over 380 patient-months, six ULH measurements were above the pre-pubertal cutoff. In spite of adequate hormonal suppression, 21 episodes of clinical breakthrough were recorded.

Conclusions: GnRHa treatment provides an adequate suppression of PP. When in doubt, both basal and post-GnRH LH levels can provide reliable data on hormonal suppression. Clinical breakthroughs during treatment do not reflect unsuppressed gonadotropins and should not lead to therapy intensification.

The Novel Chromatin Binding Protein HP1BP3 Regulates Skeletal Growth, Bone Development, Mineralization and Bone Micro-Architecture

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The decisive roles of chromatin and epigenetics in health and disease are rapidly becoming general knowledge, yet very little is known of their part in bone metabolism. We have recently discovered a novel chromatin binding protein named heterochromatin protein 1 binding protein 3 (HP1BP3). Specific antibodies we generated showed ubiquitous tissue distribution of HP1BP3 in rodents, excluding germ cells and the placenta. Phylogenetic profiling defined HP1BP3 to be a previously unknown member of the nucleosome binding histone H1 gene family. FRAP analyses of chromatin binding dynamics further confirmed the resemblance to other H1 subtypes. Generation of a knockout mouse model uncovered a range of striking phenotypes, beginning with partial postnatal lethality. Those KO pups that survive have a normal lifespan, but are growth retarded, and remain significantly shorter and lighter than their heterozygous and WT littermates. Use of micro-CT to further explore the growth retardation in femurs documented dramatic reductions in the cortical thickness and diameter of this bone in both male and female KO mice. Interestingly, an impressive 50% reduction in trabecular bone volume was observed in males only. Using the osteoblast cell line MC3T3-E1, we found that ablation of HP1BP3 by specific siRNA leads to impaired mineralization, suggesting a possible mechanism for the observed in-vivo phenotypes. Finally, we found that HP1BP3 transcriptionally regulates IGFBP-5, a key bone regulator from the IGF-1 pathway currently under study. Collectively, we show for the first time a role for a structural chromatin binding protein in bone metabolism and homeostasis.

A Patient with a Novel Mutation Causing Familial Hypocalciuric Hypercalcemia

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Background: Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal dominant disorder. The condition should be suspected in a hypercalcemic and relatively hypocalciuric patient as a differential diagnosis of PTH-dependent hypercalcemia, especially when target organ damage is not evident. The underlying pathology in FHH is a diminished sensitivity of Calcium Sensing Receptor (CASR), caused by an inactivating mutation of the CASR gene. In 2013, a novel etiology was described, mutation inAdaptor Protein 2 Sigma 1 Subunit (AP2S1), a compound that interacts with CASR, and thus is essential for calcium sensing. The condition has been named FHH-3, and is reported to occur in about 20 % of patients with FHH.

Patient: A male patient was diagnosed with hypercalcemia at the age of 15. The highest blood calcium recorded during 14 years of follow up was 12.5 mg/dl (11.45+0.48) , phosphor 3.35+0.34 mg/dl, and magnesium was mid- normal. PTH was elevated 111+56.5 pg/ml. Fractional calcium excretion calculated on several occasions was 0.01. Bone density was normal. Family members had normal blood calcium, yet FHH was strongly suspected, and the patient was followed without undergoing surgery.

Results: Analysis of the CASR gene was first performed in 2007, but no mutation was found in any of the protein-coding exons (and intron/exon boundaries). Based on the new information, analysis of AP2S1 was undertaken and the patient was positive for the mutation Arg15Cis.

Conclusion: In patients with a clinical picture suggestive of FHH and who are negative for CASR mutation, AP2S1 analysis should be undertaken.

From Base Change to Better Care in Neonatal Diabetes

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Neonatal diabetes is diagnosed in the first 6 months of life allowing separation from polygenic Type 1 diabetes. Approximately 50% of permanent neonatal diabetes have a mutation in the KATP channel. The mutated KATP channel in these patients does not close in response to increased ATP concentrations, but can be closed when sulphonylureas bind to the sulphonylurea receptor 1 subunit of the channel. These patients are usually insulin dependent, but have excellent glycaemic control on high-dose sulphonylurea tablets. Making a molecular genetic diagnosis is now recommended as soon as neonatal diabetes is diagnosed as it will completely alter the treatment used.

The advantage in treatment for the 50% of patients with potassium ATP channel mutations has resulted in every case of neonatal diabetes being referred for genetic testing when diabetes is diagnosed. Exeter offers worldwide free rapid testing for patients diagnosed before 6 months resulting in over 1200 referrals (http://www.diabetesgenes.org/).

In patients where the parents are not related predominantly de novo heterozygous mutations in Kir6.2, SUR1 and INS are found. In contrast families where the parents are related the majority of patients have homozygous mutations predominantly in EIF2AK3, Glucokinase, INS and pancreatic transcription factors including PDX1, PTF1A NEUROGENIN3,NEUROD1, and NKX2.2 .

There have been recent advances in pancreatic agenesis have the commonest cause of human pancreatic aplasia is a heterozygous mutation in GATA6 resulting in haploinsufficiency and a recessive mutation in an enhance 25KB downstream of the PTF1A gene.

The improvement in sequencing technology will result in increasing new discoveries in the 25% of neonatal Diabetes where the genetic aetiology is not known. The patient will offer crucial insights into the human beta cell, its function and development.

RFX6 a Novel Cause of Sydromic Neonatal Diabetes

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Mutations in the RFX6 gene were recently described to underlie a distinct autosomal recessive syndrome of neonatal diabetes comprising intestinal atresia and hepatobiliary abnormalities. Until now, only six patients harboring RFX6 mutations have been reported. We report on a new case due to a novel homozygous splice site mutation and update on the clinical outcome of a previously reported patient. In addition we review the clinical and molecular features of all RFX6 mutated cases to better characterize the syndrome. Our results suggest that despite the early postnatal fulminant course, patients who survive may expect a relatively favorable prognosis.

Permanent Neonatal Diabetes Mellitus due to Kir 6.2 Activating Mutation: A Long Term Follow-up

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Over the last 10 years we are following a boy with permanent neonatal diabetes mellitus (PNDM). The patient was presented at 68 days of age with severe ketoacidosis (DKA), but all three diabetes-associated antibodies were negative. An activating mutation (R201H) of KCNJ11 gene that encodes the ATP-sensitive potassium-channel subunit Kir6.2 was identified. Subsequently, insulin-pump therapy was replaced by oral glibenclamide treatment at a final dose of 2.5 mg TID, leading to a remarkable improvement in his glycemic

control. Although his weight was more than tripled over the last 10 years, glibenclamide dose was stable, therefore, his dose per weight was reduced from an initial dose of 0.8 mg/kg to 0.22 mg/kg recently. Although he consumed unrestricted diet, HgA1C levels were kept within the normal range (4.9% – 6.0%), and only when he reduced glibenclamide dose to 2.5 mg twice daily his HgA1C was increased to 9%. The child is growing consistently along the 50th percentile for height and weight, with normal cognitive and motor development. Only one episode of hypoglycemia (33 mg%) was recorded, with no episodes of DKA over the last decade. Recently we repeated a continuous glucose monitoring study and found glucose excursions quite similar to those recorded 10 years ago. During 3 days of glucose recording, glucose levels ranged from 40-70, 71-140 and 141-180 mg% 15%, 80% and 5% of the time, respectively. During nighttime blood glucose was gradually increased, reaching levels around 100 mg% at the morning. The most remarkable difference from a group of healthy controls was higher post-prandial glucose levels that reached a peak of 170 mg%.

In conclusion, 10-yeasr long glibenclamide treatment at a constant dose was safe and efficient in a child with PNDM.

The Spectrum of Neonatal Diabetes at a Tertiary Center: The Neurologic Enigma

Revital Nimri

Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel

Glucose Control of Pancreatic ß-cells

Yuval Dor

Department of Developmental Biology and Cancer Research,
The Institute for Medical Research Israel-Canada

Autophagy, Stress and the Fat-liver Axis in Obesity

Assaf Rudich

Ben Gurion University of the Negev, Beer Sheva

Regulation of Healthy Lifespan by SIRT6

Cohen Haim

Bar Ilan University, Ramat-Gan

Update on Treatment of Osteoporosis

Sundeep Khosla

Mayo Clinic College of Medicine, Department of Endocrinology

Although a number of pharmacological options are now available for the treatment of osteoporosis, appropriate risk assessment is critical to determine candidates for treatment. In the US, most current guidelines recommend treatment for postmenopausal women and men age 50 and older who have sustained a hip or vertebral (clinical or morphometric) fracture, those with T-scores below -2.5 at the femoral neck, total hip, or spine, and those with low bone mass (T-score between -1.0 and -2.5) and a 10-yr probability of hip fracture ≥ 3% or a 10-yr probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted FRAX algorithm. Currently approved drugs for osteoporosis include estrogen, raloxifene, 4 bisphosphonates, a RANKL inhibitor, and teriparatide. Most commonly used are the bisphosphonates, which generally reduce vertebral fracture risk by 40-60% and hip fracture risk by 40-50%. However, concerns regarding potential adverse effects of long-term bisphosphonate therapy, including osteonecrosis of the jaw and atypical femur fractures, have led to questions whether bisphosphonate therapy should be continued beyond 5 years and whether empiric "drug holidays" are warranted, at least in a subset of patients.

In addition to these established options for osteoporosis treatment, several drugs on the horizon provide promising new approaches. These include modulating Wnt signaling using an antibody to sclerostin and reducing bone resorption by cathepsin K inhibition. Interestingly, a combination of basic, pre-clinical, and clinical studies indicate that unlike traditional osteoporosis drugs that are either anti-resorptive or formation stimulating, both Wnt activation and cathepsin K inhibition may have "mixed" anti-resorptive/formation stimulating effects on bone. Thus, while sclerostin inhibition and subsequent Wnt activation does lead to an increase in bone formation, it also results in decreased bone resorption, leading to marked increases in bone mass over a relatively short period of time. Conversely, while cathepsin K inhibition does reduce bone resorption, the production of "clastokines" by accumulating osteoclasts on bone surfaces may sustain, or even increase, bone formation. Thus,, these compounds may be a paradigm for newer agents with both anti-resorptive and formation-stimulating capabilities in bone, leading to optimism that marked reversal of bone loss may be feasible within the forseeable future.

How Accurate Can Adrenal Imaging be in Predicting Malignancy?

Ofer Beniaminov

Institute of Radiology, Rabin Medical Center

Topics that will be addressed in the presentation:

The different modalities used for imaging the adrenal gland.

CT of the adrenal gland

MRI of the adrenal gland.

The importance of Chemical Shift Imaging in adrenal imaging.

Diffusion Weighted Imaging for the adrenal gland.

Is contrast material useful for the evaluation of the adrenal gland?

The Use of PET-CT for imaging the adrenal gland.

The most common pathologies seen on imaging and how

accurate are we in diagnosis and differentiating between benign and malignant lesions.

The Surgical Approach to the Suspicious Adernal Mass

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The surgical approach to adrenal tumors underwent a revolutionary change with the introduction of laparoscopic surgery two decades ago. Due to the many significant advantages compared to open surgery, the laparoscopic approach soon became the gold standard for small (up to 5 cm) adrenal tumors. For larger adrenal masses however, some debates still exist due to the suspected risk of malignancy and the concern of the oncological safety and the risk of tumor breakdown, during the laparoscopic procedure. Therefore, in many centers which do not specialize in advanced laparoscopic surgery, an open approach is performed for large or suspicious adrenal tumors. Primary adrenal malignancy is extremely rare, but yet the only curative chance of the patient relay on the quality of initial surgical procedure, as there is almost no curative resection for tumor recurrence. Suspicion of Adrenocortical carcinoma (ACC) should be raised when the tumor is:

1-larger than 6 cm in size with hetrogenicity, necrosis or calcifications

2-fast growing

3-locally advanced with vascular, kidney or other adjacent organs involvement, or regional lymphadenopathy

4-androgen secreting tumors are highly suspected of ACC, but also cortisol secretion causing Cushing's syndrome should be evaluated for the possibility of ACC

The surgical approach should be carefully planned according to such findings, and in high volume centers specializing in advanced laparoscopic surgery, when patient's safety and oncological surgery principles are strictly kept, such suspicious findings are not a contraindication for the laparoscopic approach as supported by several recent reports. On the other hand, for local or regional recurrent ACC, or in locally advanced lesions requiring a very extensive surgical dissection, open surgery often requiring a thoraco-abdominal incision is performed. Controlled conversion from laparoscopic to open surgery is sometimes required according to intraoperative findings.

Over the last 12 years we performed 337 laparoscopic adrenalectomies of which 49 were for tumors6 cm in size. Of these only 4 (8%) were ACC. On long term follow up, non have developed local or regional recurrence, but 2 patients developed liver metastases. During the same period of time, we performed 4 open resection for primary and recurrent ACC of which one has developed liver and one has developed lung metastases. It is our conclusion, similar to other reports, that ACC and other primary adrenal malignancy is rareeven in large or suspicious adrenal tumors, and that the laparoscopic approach was feasible and safe.

The Weiss Criteria for the Diagnosis of Adrenal Cortical Carcinoma in the Era of Molecular Markers

Grattiana Herman

Pathology Department, Assaf Harofeh Medical Center

Adrenal cortical carcinoma (ACC) is a rare tumor observed with a rate of 0.5-2 new cases/million annually. The pathological diagnosis of ACC is still challenging for its rarity and the presence of specific variants (pediatric, oncocytic, myxoid and sarcomatoid). Of the several proposed systems (Hough – 1979, Weiss – 1984, Van Slooten – 1985), the Weiss system (that analysis 9 morphologic parameters) appears to be the most utilized system even today (27 years after its proposal) because of its simplicity and reliability, and very high diagnostic performance, despite it does not reach a sensitivity and specificity of 100 % and a group of borderline cases with only one or two criteria exists with uncertain behavior. Moreover is scarcely reproducible in the ACC morphologic variants. In fact a modified Weiss system (which retained the 5 most reliable out of the initial 9 morphologic parameters) has been proposed with the aim to improve reproducibility and interobserver agreement in ACC diagnosis, and that performs better in the assessment of oncocytic variant, which seems to have a better prognosis.

Adrenal cortical tumors (ACTs) are occasionally difficult to classify in adenomas (ACAs) or carcinomas. Therefore molecular techniques such as microarray and reverse transcription polymerase chain reaction (RT-PCR) analyses have been applied in the last years, under numerous and different platforms, to overcome some of these diagnostic problems. Though the molecular/genetic pathogenesis of ACC remains an area of uncertainty and controversy, some data are available and some are quite promising, either in diagnosis improving or adding in discrimination between ACC and ACA relative to the Weiss scale, particularly for borderline tumors, either in a more accurate prognostication of the recurrence than the use of McFarlane's scale (TNM).

The Medical Approach to Adrenocortical Carcinoma

Asher Salmon

Sharett Institute of Oncology, Hadassah Hebrew University Medical School

Targeting the Human TSH Receptor – Novel Probes for Assessing TSH Physiology and Lead Drugs for Thyroid Disease

Marvin Gershgorn
Laboratory of Endocrinology and Receptor Biology, National Institute of Diabetes and Digestive and Kidney Diseases

The thyrotropin (thyroid-stimulating hormone, TSH) receptor (TSHR) is an important regulator of cell function in the thyroid gland and apparently in several extra-thyroidal sites including fat, retro-orbital tissue and bone. Moreover, TSHR appears important in the pathogenesis of several diseases including thyroid cancer and Graves' hyperthyroidism and ophthalmopathy. Although the role of the TSHR in the normal thyroid is well understood its roles in extra-thyroidal tissues, thyroid cancer and Graves' ophthalmopathy are not clear. We have developed a series of small molecule, "drug-like" compounds that are TSHR ligands. In my presentation, I will describe how we developed agonists, neutral antagonists and inverse agonists for TSHR, how we use these compounds to study extra-thyroidal actions of TSHR and what their potentials are as drugs to treat these diseases.

Protease-activated-receptors: PARtners in Physiological and Pathophysiological Processes

Rachel Bar-Shavit[1], Mohammad Jaber[1], Myriam Maoz[1], Arun Kancharla[1], Sorina Grisaru-Granovsky[1,2], Beatrice Uziely[1]
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In-addition to their classical role as digestive protein-degrading enzymes, serine-proteases can act as hormone-like molecules initiating cell signaling. This is well recognized for protease-activated-receptors; PARs activated via proteolytic cleavage of their N-terminal receptor portion. PARs are a family of G-protein coupled receptors (GPCRs), consisting of four family members, PAR1-4. PARs are expressed in the vasculature and are best known to elicit cellular responses to coagulant proteases generated during vascular injury and thrombotic diseases. Emerging evidence assign mammalian PAR1&PAR2 with central roles in breast cancer continuously activated by proteases found in the flexible microenvironment of a given tumor. A novel pleckstrin-homology (PH) domain binding site was allocated to both PAR1 and PAR2 as an early signaling event. This was shown by the selective co-association of either Etk/Bmx as also other signaling partners such as Akt and Vav via their PH-domain. The minimal C-tail binding sequence to the PH-domain was identified in both PARs as a potential platform for future therapeutic medicaments to silence PARs. Assessment of pro-tumor and physiological invasion functions of the PARs using the approach of shRNA-hPar2 knocked-down hPar2 as also a non-functional PAR2, devoid the entire cytoplasmic tail demonstrated the dominant role of PAR2 in tumor biology. Collectively, these findings indicate that hPar2 expression is required for thrombin induced pro-tumor processes. The non-functional PAR2 inhibited PAR1-PAR2-driven tumor growth in vivo and the interaction of Etk/Bmx with the PAR1-C-tail in vitro. Confocal images demonstrated co-localization of PAR1 and PAR2 in HEK293T cells over-expressing YFP-hPar2 and HA-hPar1 and co-immunoprecipitation analyses showed stable PAR1-PAR2 complex formation. Physiological invasion of placenta extravilous trophoblasts was also attenuated by silencing of PAR2. Taken together, PAR1 and PAR2 act as one functional heterodimer unit in tumor development and placenta - uterus interactions.

G-Protein Coupled Receptors and Their Ligands: Selectivity and Promiscuity

Masha Niv

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G-protein coupled receptors (GPCRs) constitute a large family of seven-transmembrane proteins located at the plasma membrane. Much of the information from other organs and from the outside world is processed by GPCRs, which respond to a broad spectrum of chemical entities, ranging from small protons to large glycoproteins. As such, they have a central role in health and disease, and are major targets of therapeutic drugs.

Dramatic chemical diversity may occur even among ligands of the same receptor, as in the case of bitter taste receptors. This subfamily of GPCRs mediates aversive reaction to bitter and potentially toxic foods. Bitter taste receptors were shown to express also extraorally, i.e. in the gastrointestinal tract and in the male reproductive system. The elucidation of novel physiological roles and identification of tissue-relevant ligands are currently underway and raise fundamental questions: How can one GPCR interact with chemically diverse ligands? What makes some GPCRs more promiscuous than others?

We found that the use of partially overlapping sets of positions within the main binding pocket, and employment of different types of interactions of the same residues are the molecular scenarios that enable binding of dissimilar ligands by the same bitter taste receptor. A comprehensive analysis of family A GPCRs, unraveled general features that correlate with diversity of ligands and can successfully predict the promiscuity of unrelated GPCRs. This provides novel insights and tools for GPCR-centered drug design.

Rickets Update 2014

Eli Hershkovitz

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The Role of Angiogenesis in the Selection of Dominant Follicles in the Mouse Ovary

Liat Alyagor, Michal Neeman, Nava Dekel

Biological Regulation, The Weizmann Institute of Science

Dominant follicles (DF) acquire their selective advantage by creating richer vasculature that allows the accumulation of higher hormone concentrations. However, the mechanisms that drive this angiogenic capacity of the DF are yet to be revealed. Since, the PI3K/AKT1 pathway has an important role in regulating angiogenesis, we assumed that activation of AKT1 in endothelial cells could cause an extensive angiogenic reaction resulting in the selection of a larger number of DF. Additionally, the DF may secrete anti-angiogenic factors to induce atresia of the subordinate follicles. This study aimed at characterizing the role of endothelial AKT1 and anti angiogenic factors in DF selection. Preliminary results in a transgenic mouse model that express myristoylated AKT1 (myrAKT1) in endothelial cells showed increased expression of CD34 (a marker for newly formed blood vessels) around follicles. However, no difference in ovulation rates was found. Analysis of mRNA from whole ovaries by qRT-PCR showed a significant increase in soluble vascular endothelial growth factor receptor 1 (sFlt) mRNA expression 5, 36 and 48 hours after PMSG injection. A further increase was observed 4 and 12 hours after hCG injection. We show that endothelial myrAKT1 causes an angiogenic reaction around follicles. However the effect of this phenomenon on fertility is to be discovered. Furthermore, these results support our hypothesis regarding anti angiogenic factors secretion from the DF to their surroundings. Further study is needed to establish sFlt role in DF selection. Understanding the mechanisms of DF selection can help improve assisted reproductive technologies and promote fertility disorders understanding.

Reproductive Hormone under Tension: Regulation of Gene Expression through Nucleosomal Dynamics

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Luteinizinghormone (LH) plays a distinct role in stimulating growth, gametogenesis and steroidogenesis of the gonads. The expression of the LHβ-subunit is activated by the gonadotropin-releasing hormone (GnRH) which overcomes LHβ gene repression. To overcome this repression, the promoter has to be accessible for the transcription machinery which is achieved by removal or repositioning of the nucleosomes in this region. Various factors influence nucleosome positions, including histone modifications and binding of transcription factors (TFs). It has been previously demonstrated that GnRH upregulates various specific transcription factors including Egr-1, which along with SF-1 and Pitx-1 activates LHβ transcription. Additionally, GnRH regulates LHβ transcription at the chromatin level, through displacement of histone deacetylases, thereby allowing histone acetylation. We hypothesize that transcriptional activation of the LHβ gene by GnRH involves nucleosome repositioning on its promoter. To test this hypothesis, we combine single-molecule optical tweezers experiments to obtain changes in nucleosomal structure and dynamics, together with experiments in gonadotrope cell lines. Using MNase-qPCR analysis we characterized the nucleosome positioning in the LHβ gene promoter in gonadotrope cells and found that GnRH exerts a nucleosome positioning effect. We performed chromatin immunoprecipitation studies and found an increase in Egr-1 occupancy on the LHβ promoter and observed Histone 3 Lysine 56 acetylation after 1 h of GnRH, possibly suggesting their involvement in the nucleosome positioning effect. These results suggest that transcriptional activation of the LHβ by GnRH involves nucleosome repositioning in the promoter through upregulation of TFs and histone modifications.

The Role of Interleukin-1 in Reproductive Aging in Mice

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Oocyte endowment dwindles away during pre-pubertal and adult life until menopause occurs and apoptosis is identified as a central mechanism responsible for oocytes elimination. A few recent reports suggested that uncontrolled inflammation may adversely affect ovarian reserve. We tested the possible role of the pro-inflammatory cytokine Interleukin (IL)-1 in the age related exhaustion of ovarian reserve using IL-1α and IL-1β knock-out (KO) mice. IL-1α-KO mice showed a substantially higher pregnancy rate and litter size compared to WT at advanced age. The number of the secondary and antral follicles was significantly higher in 2.5 month old IL-1α-KO compared to WT ovaries. Serum anti-mullerian hormone (AMH), a putative marker of ovarian reserve, was markedly higher in IL-1α-KO mice from 2.5 months onwards, along with a greater ovarian response to gonadotropins. IL-1β-KO mice displayed a comparable but more subtle prolongation of ovarian life-span compared to IL-1α-KO mice. The protein and mRNA of both IL-1α and IL-1β were localized within developing follicles (oocytes and granulosa cells) and their ovarian mRNA levels increased with age. Molecular analysis revealed a decreased apoptotic signaling (higher BCL-2 and lower Bax protein levels) along with a marked attenuation in the expression of genes coding for the pro-inflammatory cytokines IL-1β, IL-6 and TNFα in ovaries of IL-1α-KO compared to WT mice. Taken together, IL-1 emerges as an important participant in the age related exhaustion of ovarian reserve in mice possibly by enhancing the expression of inflammatory genes and promoting apoptotic pathways.

The Role of Vasorin under Hypoxic and Oxidative Stress Conditions in Mouse Ovaries

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The ovary is a metabolically active organ, which changes periodically during the reproductive lifespan. As a result, the female gonad is subjected to a variety of stress conditions, including hypoxia, derived from poor vascularization that is associated with advanced stages of folliculogenesis, and oxidative stress, which is consequent to high production of reactive oxygen species (ROS) associated with ovulation. However, the regulatory mechanisms of these processes are yet to be elucidated, as a possible member of such regulatory mechanisms, we suggest Vasorin/ATIA (Vasn), a type I membrane protein. Vasn is a target of hypoxia inducible factor (HIF)-1, which is expressed in the mitochondria and allows the antioxidant thioredoxin 2 (TRX2) to protect cells from TNFα and hypoxia-induced apoptosis. Our initial results demonstrate that Vasn is expressed by the granulosa cells during folliculogenesis and its expression is up-regulated in response to the preovulatory surge of luteinizing hormone (LH). Therefore, we hypothesize that Vasn may be involved in ovarian physiology and possibly play a role in protecting ovarian cells from hypoxic and/or oxidative damage. To test this hypothesis we plan to examine abnormalities in morphology and mitochondrial ROS production in ovaries of Vasn knockout mice, during folliculogenesis, ovulation and ovarian aging. We will also characterize mitochondrial expression of Vasn in mouse ovaries and identify oxidative stress related proteins that interact with this protein. Our results will potentially shed light on a hitherto unexplored ovarian regulatory component.

Change and Synchronization of Birth Seasonality in Jews and Muslims of Israel (1971 - 2010) affected by socio-economic factors

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Background: Human populations show seasonal patterns of birth rates, which are stable in any particular population, but vary widely across geographical locations and different populations.

These differences have been attributed to climatic factors, yet additional factors have been proposed. We report how in two populations sharing the same geographical location and environmental conditions, one population is changing and synchronizing its seasonal patterns of birth, to resemble the other population.

Methods: Monthly birth rates were extracted from the Israel Central Bureau of Statistics, and corrected for month length and de-trended using a moving average of 12 months. These were compared with climate, Ramadan, and socio-economic changes: number of children, education, and profession.

Results: Over the last 40 years the monthly birth fluctuations of the Jewish and Muslim populations in Israel changed from qualitatively different patterns to similar ones. The peak birth rate of the Muslim population moved from winter to late summer, resembling the Jewish pattern, whereas the Jewish seasonality remained stable. These changes could not be attributed to climate, religious holidays, or marriage seasonality.

Conclusions: We suggest that the synchronization of Muslim birth seasonality, changing in 40 years to resemble Jewish birth seasonality, is probably due to the urbanization of Muslim population, as can be seen in changes in education, profession, birth rate, etc.

Changes in seasonal patterns have implications for health services and for research proposing season of birth as a risk factor in various disorders.

Pigment-epithelium-derived-factor (PEDF) is Dynamically Expressed in the Human Endometrium

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The endometrium exhibit morphological and functional changes in response to the fluctuating estrogen (E2) and progesterone (P4). We have characterized Pigment-epithelium-derived-factor (PEDF) expression in the reproductive system and its hormonal regulation in the ovaries, which was found to be inversed to vascular-endothelial-growth-factor (VEGF). We therefore aimed to explore in this study the hormonal regulation of PEDF in the endometrium. We found that both human and mouse endometrium expressed PEDF. This expression was significantly affected by E2 and P4 both in-vivo and in-vitro; E2 decreased PEDF expression while P4 increased it. In human endometrial samples, PEDF levels were dynamically altered along the menstrual cycle; low at the proliferative and early secretory phases and significantly higher at the late secretory phase, exhibiting an inverse pattern to VEGF expression.

Finally, we showed that PEDF receptor is expressed in the endometrium and that stimulation with rPEDF reduced VEGF expression. By illustrating the pattern of PEDF expression during the menstrual cycle we may contribute to the understanding of the endometrial complexity.

Primary Human Vascular Smooth Muscle Cells are Target for the Mutual Modulatory Effects of the Selective Estrogen Receptor Modulator, Femarelle and a Vitamin D Analog

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To assess the modulation by "less-calcemic" analog of 1,25(OH)2D3 (1,25D); JK 1624F2-2 (JKF) on estrogenic effects on human vasculature, we compared Femarelle (F), daidzein (D) and estradiol-17b (E2) effects on DNA synthesis and CK specific activity in human VSMC. F, D and E2, stimulated VSMC DNA synthesis at low, and suppressed it at high concentrations. Yet they dose-dependently increased CK activity. Daily treatment with JKF (1nM for 3days) decreased DNA synthesis, increased CK activity and up-regulation of the stimulation of DNA synthesis by low concentrations of estrogen-mimetic compounds. F-induced inhibition of VSMC proliferation was unchanged by JKF while, D- and E2-inhibition was abolished by JFK. Additionally, JFK upregulated the stimulatory effects of all compounds on CK. VSMC express ERa and ERb mRNA (ERa to ERb 2.7: 1.0). JKF pretreatment increased ERa (~30%) and decreased ERb (~50%). E2 had no effect and D and F upregulated both. JKF increased intracellular competitive binding of F (~90%), D (~60%) and E2 (~110%). F reciprocally modulated vitamin D system by upregulating mRNA expression of vitamin D receptor (VDR) and 25 hydroxyy vitamin D 1-a hydroxylase (1OHase) and stimulated 1OHase activity by increased 1,25D production (~120%) as well as D (~90%). In conclusion, human VSMC growth (DNA synthesis) and metabolic activity (CK) are modulated by F and vitamin D analogs. The estrogenic effects on VSMC depend on the concentration and nature of the compounds, due to their binding to different ERs. Moreover, since F reciprocally modulated the vitamin D system, it might comprise an attractive candidate for hormone replacement therapy for vascular protection.

Pituitary Imaging Findings in Male Patients with Idiopathic Hypogonadotrophic Hypogonadism

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Introduction: Central hypogonadism in the presence of normal olfaction and no known pituitary disease is termed idiopathic hypogonadotrophic hypogonadism (IHH). Data on pituitary imaging in patients presenting with IHH are scarce.

Objective: To assess the usefulness of pituitary imaging in the evaluation of men presenting with IHH after excluding known pituitary disorders and hyperprolactinemia.

Patients and methods: A retrospective review of clinical and pituitary imaging findings of men who presented for endocrine evaluation with IHH from 2010-2013. Patients with testosterone levels 10.4nmol/L (300ng/ml) and normal LH and FSH levels were included.

Results: Sixty six men were included in the analysis. Their mean age and BMI were 53.3±14.6 years and 30.6±5 kg/cm2, respectively. Mean total testosterone, LH, and FSH were 6.2±1.8nmol/L, 3.2±1.9 and 4.6±3.1mIU/L, respectively. Prolactin level within the normal range was obtained in all men (mean 161±61, range 41-347 mIU/L). Fifty four men had pituitary MRI and 12 performed CT. In 49 men (74.2%) pituitary imaging was normal. Microadenoma was found in 8 (12.1%). Empty sella and thickened pituitary stalk in 1 patient (1.5%), each. In additional 7 patients (10.6%), a small or mildly asymmetric pituitary gland was noted. No correlation was found between testosterone level and the presence of pituitary anomalies.

Conclusions: This study does not suggest that the use of routine hypothalamic-pituitary imaging in the evaluation of IHH, in the absence of clinical characteristics of other hormonal loss or sellar compression symptoms, will increase diagnosis of structural abnormalities over that reported in the general population.

Women with Prolactinomas Presented at the Postmenopausal Period

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In women microprolactinomas are commonly diagnosed between 20-40-year-old. In postmenopausal women prolactinomas are rarely encountered, and usually do not present with hyperprolactinemia-related symptoms as these are dependent on intact ovarian function. We have summarized our experience with 14 consecutive postmenopausal women (mean age, 63.6+7.1 years; range, 54-75 years) diagnosed with prolactinomas. Mean adenoma size at presentation was 25.6+12.4 mm (range, 8-50 mm). Six out of the 14 women had significant visual fields damage at presentation. Mean baseline PRL level was 1,783 ng/ml, and median PRL was 827 ng/ml (range, 85-6,732 ng/ml). Medical treatment with cabergoline was given to twelve of the females. Cabergoline normalized/near-normalized PRL in eleven women; one woman was dopamine agonist-resistant. Five of the six subjects with visual disturbances normalized or improved their vision, and a pre-treatment diplopia in another patient disappeared. Two large pituitary tumors disappeared on MRI following long-term dopamine agonist therapy. All other treated prolactinomas, beside the resistant adenoma, shrank following medical treatment.

In conclusion, prolactinomas are rarely diagnosed in postmenopausal women. These women usually harbor large and invasive adenomas, secreting high PRL levels, and usually respond to dopamine agonist treatment.

Hypopituitarism Patterns and Prevalence among Men with Macroprolactinomas

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Objective: Men with prolactin secreting tumors usually harbor macroadenomas. The degree of pituitary dysfunction may vary among different adenoma size subgroups, as is recovery after treatment. Our study objective was to characterize hypopituitarism and recovery after treatment in men with macroprolcatinomas.

Design: A retrospective study, including a consecutive group of men with pituitary macroadenomas (u style="font-weight: normal;"10 mm) and hyperporlactinemia (10xULN).

Methods: Patients were divided into three categories according to adenoma size at presentation: 10-19 mm (group A), 20-39 mm (group B), and u style="font-weight: normal;"40 mm (group C). We compared total testosterone, gonadotropins, cortisol, thyroid hormones and hemoglobin levels at presentation and after treatment.

Results: Eighty three patients were included; 26, 31 and 26 patients in groups A, B and C, respectively. Pretreatment hypogonadism prevalence was 72.7%, 93.5% and 90.9%, (p=0.022; A vs B & C), central hypocortisolism - 0%, 6.9% and 33.3% (p=0.005), and central hypothyroidism – 6.3%, 17.9% and 26.1% (NS) in groups A, B and C, respectively. Only 26.2% of all patients presented with hypocortisolism and/or hypothyroidism (42.9% in group C). Anemia (Hb 13.5 gr%) was detected in 31.6%, 57.1% and 80.0% in groups A, B and C, respectively (p=0.04). FT4 levels at presentation had strong positive correlation with post treatment FT4 levels (r=0.45, p=0.035). Larger adenoma diameter correlated strongly with lower FT4 levels following treatment (r=-0.42, p=0.043).

Conclusion: Macroprolactinomas in men caused partial hypopituitarism, affecting testosterone and cortisol more in patients with larger adenomas. However, most of the men did not have pituitary hormones affected, beside testosterone.

Metabolic Paradox in AHNAK KO Mice

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AHNAK is a protein that is elevated in obesity. To understand the role of AHNAK in metabolic homeostasis we utilized AHNAK-knockout (KO) mice. AHNAK-KO mice were protected from HFD induced obesity(DIO) reflected by a marked reduction in adipose tissue mass (50%), reduced body weight (25%) and increased lean body mass (37%) compared to the wild type (WT) mice on HFD. KO-HFD mice exhibited insulin resistance (IR) as assessed by glucose/insulin- tolerance test. Compared to the WT-HFD mice, fasting blood glucose levels were elevated in the KO-HFD (143mg/dL and 168mg/dL) while plasma insulin levels were lower (4.3 and 2.7ng/mL respectively). Glut4 levels in adipose tissue from KO-chow or HFD were reduced (35% and 20% vs 100% WT-chow) and in skeletal muscle obtained from KO-HFD mice, a 50% reduction was observed compared to WT-chow mice. Akt phosphorylation was impaired (70-80% reduction) in adipose, skeletal muscle and liver tissues of WT and KO mice on HFD and a 50-70% reduction in pAkt was observed in KO-chow mice. Gene expression studies showed 4-fold increase of SCD-1, in the adipose tissue, muscle and liver and 2-fold increase of RBP4, in the adipose tissue in KO-HFD. PGC1α was reduced in both adipose tissue and liver of KO mice. IGFBP1 was elevated in KO mice on regular chow while being suppressed in KO mice on HFD. Thus we demonstrate (a) under normal feeding AHNAK-KO mice are hyperglycemic and insulin deficient (b) AHNAK deletion protects against DIO, but not against HFD-induced IR and glucose intolerance in vivo.

Blinded Continuous Glucose Monitoring During Yom Kippur Fast in Adult Type 1 Diabetic Patients on Insulin Pump Therapy

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Rationale: Jewish Type 1 diabetic (T1DM) patients who intend to fast on Yom Kippur are advised to consult their diabetologist about the feasibility of fasting. In the past, most patients were not allowed to fast, however well-controlled patients on basal-bolus insulin regimen or on insulin pump therapy (CSII), can try to fast after receiving individualized instructions.

Aim: Our aim was to record by blinded continuous glucose monitoring (CGM) the glucose values in 10 T1DM patients willing to fast for 25 hours on Yom Kippur, and to analyze the data with emphasis on significant hypoglycemic or hyperglycemic episodes.

Subjects and methods: 10 male adult T1DM patients, currently on CSII and willing to fast on Yom Kippur, were recruited. HbA1C above 9%, high risk of dehydration, recent severe hypoglycemia or keto-acidosis were exclusion criteria. The patients were advised to decrease their bolus dose by 20-40% for the pre-fast meal and to decrease their basal rate by 20-40% during the fast. Blinded CGM was performed during the fast, and patients filled a concomitant diary recording capillary blood glucose values, food, hypoglycemic symptoms and unusual events.

Results: No clinical episodes of severe hypoglycemia or hyperglycemia were observed during the fast, suggesting that basal rate should be decreased by 30-40% for safe fasting. In some patients, real-time availability of the CGM data analyzed retrospectively could have contributed to better control during the fast.

Conclusion: Our pilot study suggests that 25-hour fasting is feasible in a selected population of T1DM patients well controlled on CSII.

The Role of Growth Hormone on ß-cell Function and Regeneration

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Type 1 diabetes (T1D) is an autoimmune disease. It is characterized by loss of pancreatic ß-cell mass, which results in dramatic reduced serum insulin levels. ß-cell mass is determined by the number and the size of its pancreatic ß-cells. The relationship between growth hormone (GH), insulin like growth factor (IGF)-1 and insulin, has been suggested in controlling ß-cell function and replication. Over expression of IGF-2 in the mouse, results in islet cell hyperplasia in the fetal pancreas, while specific over expression of IGF-1 in ß-cells postnatally results in ß-cell proliferation. Recently it was demonstrated that GH works synergistically with IGF-1 to prevent ß-cell death, and elevates ß-cell mass and function.Following our previous demonstration that specific growth hormone receptor knock out in ß-cells (ßGHRKO) affects compensatory hyperplasia induced by high fat diet, we induced diabetes in 12 weeks old mice with streptozotocin (STZ). GH treatment resulted in weight gain and normalization of their blood glucose level. Moreover, pancreatic hematoxylin and eosin (H&E) staining from these mice demonstrated recovery of the damaged islets i.e. the islets were larger in diameter and had a significantly higher area and with more nuclei, as well as recovery of serum insulin, suggesting GH treatment might block the deteriorating state of T1D perhaps through hyperplasiaof the islets.

Impairment in Glucose Homeostasis among Adolescents in High Risk Diabetes Prone Population

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Background: Obesity is increasing worldwide among adults, children and adolescents. The increase in obesity rate paved the way for the development of several morbidities including impairment in glucose homeostasis. This is why the frequency of Type 2 Diabetes Mellitus (T2DM) is increasing among children and adolescents. T2DM is described mainly among minority groups, and in Israel it is more frequent among the Arab population.

Working hypothesis: Among obese children and adolescents that belong to a high risk diabetes prone Arab population, there is a subgroup with impaired glucose homeostasis.

Aims: The aim of the study was to identify patients who have impaired glucose metabolism, for diagnosis and treatment.

Methods: 120 (78 girls, 42 boys), obese (BMI percentile 95, BMI 30) children and adolescents,10-18 years old , from an Arab village in Israel were studied. Most patients of this village belong to two families who have a high incidence of obesity and T2DM. All patients had a physical exam and their body composition and metabolic status were evaluated.

Results: Mean age was 13.5 ± 2 y. Mean BMI percentile was in the 97th percentile. T2DM was present in 33% of parents and 60% of grandparents. Mean fasting blood glucose was 95±13. Two girls were diagnosed with T2DM, 16.2 % had impaired fasting glucose, and 56.5% had prediabetes by HbA1C definition (5.7%). HOMA-IR was higher in boys than in girls (6.04±4 vs. 7±6, respectively).

Conclusions: In obese children and adolescents from a high risk population impairment of glucose homeostasis is common. Identifying these children can prevent future morbidity.

Exercise First, Diet Later: Exercise Prior to Diet Protects Subjects with the Metabolic Syndrome from Muscle Loss, Independent of Age/Gender

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Recommended treatment for metabolic syndrome (MetS) patients is a combination of proper diet with exercise. Most attempted weight loss periods terminate in subsequent weight regaining. Muscle loss during diet occurs often, thus repeated weight loss attempts could lead to increasing sarcopenia, frailty and disability. Here we assessed the effect of a 1 year multidisciplinary intensive intervention program on body composition and metabolic outcome.

Methods: thirty eight patients that completed 1 year of intervention involving frequent interaction with physicians, a dietician and physiologist. Patients' ages were 19-71y, median age ~53. Nine men and 8 women were above and 12 men and 6 women below median age.

Results:

		<53yrs	>53yrs
% weight loss	Women	11	6
	Men	10	6.5
%lean loss	Women	5	3
	Men	1	3
%fat loss	Women	17.5	10
	Men	17	15

Strikingly all subjects that gained or lost less than 2.9% lean (median value of % lean loss) were exclusively those engaged in physical activity prior to intervention, and continued throughout this year (χ^2, p0.001).

Conclusions: During intensive weight loss supervised by a multidisciplinary team according to current "best practice" guidelines: a) young and older men can lose weight without obligatory lean mass loss; b) young and older women tend to lose lean mass (muscle), along with fat loss, unless they engaged in physical activity prior to the attempted weight loss. We submit that to preserve muscle in MetS, irrespective of age, exercise should precede the initiation of weight loss and not be started coincident with diet.

Does the Frequency and Severity of Sleep Disordered Breathing in Obese Children with and without Type 2 Diabetes is Different?

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Background: Obstructive sleep apnea (OSA) is a risk factor for insulin resistance and type 2 diabetes mellitus (T2DM) in adults. Data in children is limited.

Aims: To study the frequency and severity of OSA and its association with cardiometabolic risk factors in obese children and adolescents with and without T2DM.

Methods: Obese patients with and without T2DM underwent polysomnography and blood tests for fasting lipids, insulin, glucose, liver functions, and C-reactive protein. All participants completed a questionnaire on past and present sleep-disordered breathing (SDB). Results were compared between T2DM and obese non-diabetic controls matched for body mass index-standard deviation score (BMI-SDS) and according to the glycemic status: T2DM, impaired glucose tolerance (IGT) and normal glycemic control.

Results: Eleven patients with T2DM (age 15.9±3.6 years) and 30 obese non-diabetic subjects (age 12.7±3.0 years) were studied. Among the entire cohort, 45% had a history of snoring, 26% reported apneic episodes during sleep; 65% had daytime fatigue. There were no significant between-group differences in SDB history or abnormal polysomnographic results. A trend towards higher incidence of abnormal polysomnography was observed in association with the severity of the glycemic abnormality (45.5% in T2DM patients, 25% in obese patients with IGT, and 18.2% in obese patients without IGT). Plasma CRP levels were related to both glycemic status and OSA severity.

Conclusions: The severity of OSA in obese children is unrelated to the presence of diabetes. OSA may play a minor role in the development and progression of T2DM in children. Further studies in larger cohorts are required.

Possible Short Acting Insulin Analogues Instability as a Cause of Hyperglycemia and Diabetic Ketoacidosis in Diabetic Insulin Pump Users

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Introduction: Short acting insulin analogues are widely used via injections or insulin pumps in therapy of diabetes mellitus. Their stability may be changed due to various parameters. Aim: To describe patients who developed hyperglycemia and\or diabetic ketoacidosis due to possible short acting insulin analogues instability.

Patients: 6 patients developed hyperglycemia while on insulin therapy by short acting insulin analogues via insulin pumps. 3 developed diabetic ketoacidosis which mandatory hospitalization. None had any pump failure. All recovered with short acting insulin use.

Conclusion: Short acting insulin analogues may be instable and cause hyperglycemia and\or diabetic ketoacidosis. We suggest that short acting insulin analouges users should have regular insulin at hand for possible failure of their insulin use.

Short and Long-term Outcome of Differentiated Thyroid cancer (DCT) Patients with Lymph Nodes (LN) Involvement

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Introduction: Cervical LN metastases are a strong predictor for persistent disease in DCT patients.

Aims: To investigate predictive factors that correlates with improved outcome in DCT patients with LN metastases.

Methods: From the Rabin Medical Center Thyroid Cancer Registry we identified 183 patients with N1 disease out of 800 operated since 1995 having sufficient data for analysis. All patients were treated with total thyroidectomy and RAI. Lateral ND was performed in 52%, central ND in 27% and no formal ND in 21%. Partial thyroidectomy, distant metastases and poor differentiation were exclusion criteria. Follow-up period was 8 years.

Results: Mean age at diagnosis was 46.5±15, 70% were females, 93% had PTC/PTCFV, 60% were T1-2 and 42% had extra-thyroid extension (ETE). The median number of LN affected/excised was 4/12 (1-2 LN were excised in 24%). Median size of largest LN was 15 mm. By inclusion criteria all patients were N1 (N1a 48% and N1b 52%). Mean RAI first dose was 142+32 mCi. At 1 year post-treatment, 82/183 (45%) patients had persistent disease (23 biochemically only). Factors associated with persistency were gender, primary size, focality, ETE, N1b, LN yield, LN size and postOp stTg. At last follow-up 25/79 patients had NED and this was associated with the size of the primary tumor, postOp and 1-yr stTg and the cumulative I-131 dose.

Conclusion: Extension of disease, stTg levels and cumulative I-131 dose (but not first dose) were associated with persistency in patients with lymph node involvement

The Effect of Radioactive iodine (131I) Treatment on Ovarian Reserve: Preliminary Data from a Prospective Study

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[2]*Racine IVF Unit, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center*
[3]*Radiation Therapy Unit, Institute of Oncology, Tel Aviv Sourasky Medical Center*

Differentiated thyroid carcinoma and thyrotoxicosis are commonly diagnosed in women in their reproductive years. Despite some reports suggesting an earlier age at menopause, the full impact of RAI treatment on gonadal reserve has never been systematically studied. The aim of this study is to prospectively evaluate the effect of RAI therapy on ovarian reserve as assessed by the level of anti-Mullerian hormone (AMH).

Study Design: This prospective study aims at enrolling 30 patients, between the ages of 18-45 years, scheduled to undergo RAI treatment. Serum AMH, estradiol and gonadotropins are assessed at baseline, and every 3 months for a year following RAI treatment. While each subject serves as her own control, AMH levels will also be compared to the expected decline over time.

Preliminary Results: Ten patients, aged 20-40 have been enrolled in the study so far. All had regular menstrual periods before treatment. Five women had borne children. Seven women received RAI for papillary thyroid cancer at doses between 30-150 mCi. Three patient received treatment for Graves' disease (10-18 mCi). The levels of AMH in the patients before the RAI treatment were 1.3 – 6.9 ng/ml. At 3 months, they decreased by more than 50% in 2 patients who received 150 mCi RAI (from 5.9+1.3 to 2.0+0.06).

Conclusions: If confirmed, these preliminary data would suggest an early deleterious effect of RAI on ovarian reserve. This could potentially affect treatment decision particularly in young women with thyroid cancer.

One Euthyroid Range for Healthy, Ambulatory People Living Anywhere in Israel

Lawrence Levene

Marketing, Tayco Diagnostics

Around 2.5 million thyroid tests/year are run in Israel with at least 14 different reference ranges reported by the laboratories. Nearly 2 million of these tests are run on the same analyzer, from Siemens Healthcare Diagnostics. Using the results from the large, regional laboratories and applying the same exclusion criteria, it is possible to derive a very significant number of thyroid results (about 1 million) for a "healthy" population. By applying various statistical protocols to analyze the data, one can arrive at one reference range that could be applicable for the majority of our population. This range can be verified in one of the regional labs and if appropriate, adopted by all the laboratories using the Siemens analyzer, irrespective of the HMO to which they belong. If there are sufficient data, one can also derive age-related ranges, e.g pediatrics and the elderly.

First Trimester TSH and Future Development of Thyrotoxicosis

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[2]*Clincal Research Center, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev*
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Introduction: Low TSH levels during pregnancy may result from transient HCG thyrotoxicosis or first presentation of Graves disease. Our aim was to find predictors of future thyrotoxicosis in women with a low TSH in first trimester.

Methods: Medical records of women who delivered singleton at Soroka-Medical-Center between 1/2001-12/2011 and had a TSH4.0 mIU/L during the first trimester were screened for future thyrotoxicosis, defined as TSH0.4 or thyrotoxicosis on further testing. Women with hypothyroidism or hyperthyroidism prior to pregnancy were excluded.

Results: We identified 3,928 women with first trimester TSH4.0 and one additional TSH measurement and stratified by TSH level into four groups: TSH0.1 (207, 5.2%), 0.21-0.2 (99, 1.42%), 0.21-0.4 (214, 5.4%) and 0.41-4.0 (3408, 86.7%). Total of 210 women (5.3%) developed thyrotoxicosis: 24%, 16.2%, 10.3% and 3.6% in the four groups respectively.

When available (n=449), mean first FT4 was higher (1.58±0.57 pg/L vs.1.23±0.26 pg/L) and median first TSH was lower (0.65 vs. 1.48) in women with thyrotoxicosis (P0.001 for both). Among women with TSH 0.1 in first trimester FT4 was significantly higher in those who developed future thyrotoxicosis (1.85±0.62 vs. 1.45±0.36 p0.001). Multivariate analysis showed an odds ratio of 8.7 (p0.001) to develop thyrotoxicosis comparing women with first trimester TSH0.1 to those with a normal TSH (0.4).

Conclusions: Thyrotoxicosis incidence was significantly higher in women with a first trimester TSH0.1 and much less in the 0.1-0.2 group. Levels of FT4 were a strong predictor of thyrotoxicosis in women with TSH0.1.

Majority of women with low TSH in early pregnancy recovered to normal thyroid function on follow-up.

Obstetric and Endocrine Outcomes According to First Trimester TSH Levels

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[2]*Clinical Research Center, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev*
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Introduction: Thyroid function is commonly assessed during first trimester. The association between early pregnancy maternal serum TSH and pregnancy outcome was assessed. Methods: Electronic medical charts of women who delivered at Soroka-Medical-Center from 1/2001to 12/2011 who had TSH4.0 during the first trimester were screened. Women were divided into four quartiles of maternal TSH concentrations according to gestational age. Women with diagnosis of hypo or hyperthyroidism prior to pregnancy or with multiple gestations were excluded. Obstetrical outcomes, HCG concentrations and future thyroid status were assessed according to TSH quartiles.

Results: Our cohort included 14,357 women who met inclusion criteria. TSH distribution during first trimester is presented in the Figure. First TSH0.4 was found in 9.5% of women: 3.1% TSH0.1, 2.1% TSH0.1-0.2, 4.3% TSH0.21-0.4. Mean βHCG (adjusted for gestational age) was higher in the lowest TSH quartile. Rate of prior preterm delivery and pre-eclampsia was increased in the first and second TSH quartiles. There was no significant difference in obstetric outcomes including preterm delivery, SGA neonate, gestational diabetes or mode of delivery among the TSH quartiles. Female gender was more frequent in the lowest TSH quartile. In women with additional TSH measurements, thyrotoxicosis was diagnosed in 246 (1.7%).Multivariate analysis showed the lowest TSH quartile had an odds of 3.0 to develop thyrotoxicosis compared to the highest quartile (P0.001).

Conclusions: We describe TSH distribution in first trimester. Women in lowest TSH quartile did not differ in obstetric outcomes from those in higher quartiles but had more female babies. Future thyrotoxicosis was rare even among women in the lowest TSH quartile. tsh0.2,

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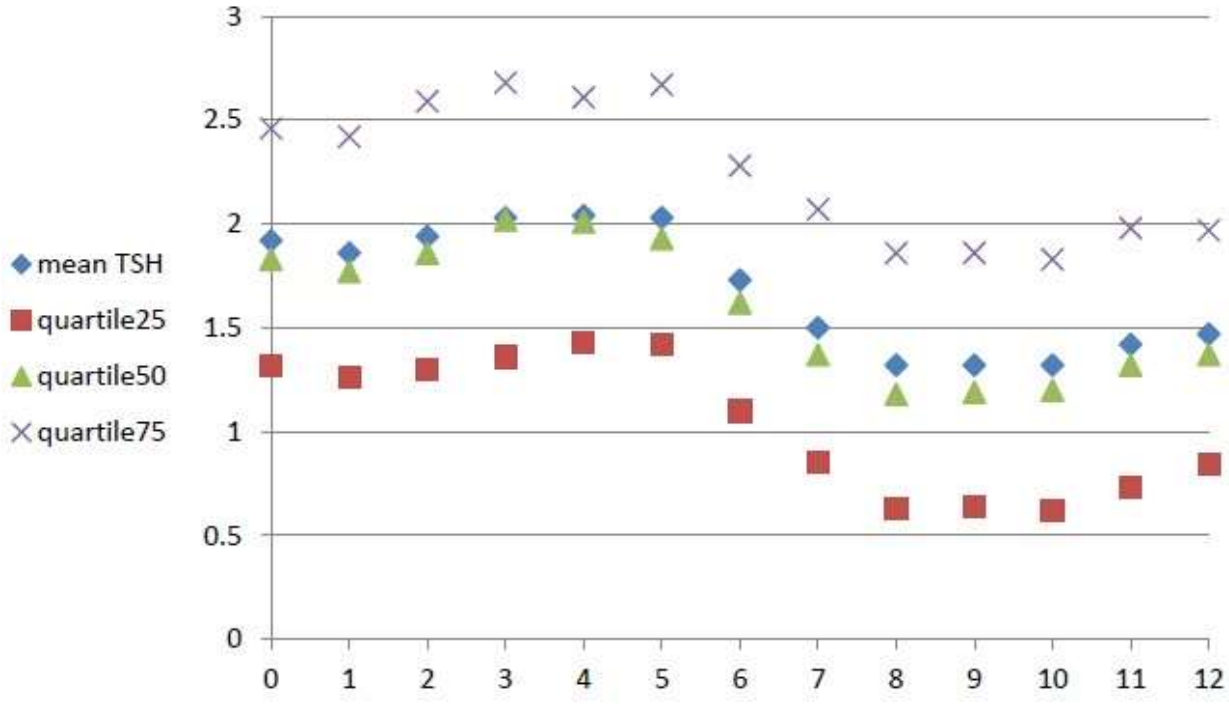
mean TSH
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Euthyroid Humans Thyrotropin Enhances Throxine Conversion to Triiodothyronine

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[4]*Jerusalem, Israel, Hadassah-Hebrew University Medical Center*

Introduction: About 80% of triiodothyronine (T3) production is due to extrathyroidal conversion of T4 to T3 by two deiodinases (D1 and D2). The influence of TSH on deioidinase activity has been shown in thyroid cell cultures. Whether this effect is significant in-vivo is not known.

Methods: We have studied 3,412 results of free T3(FT3), free T4(FT4) and TSH of healthy children (ages of 1- 20 yr) without any known thyroid disease. This provided the opportunity to investigate the effects of TSH on production of T4 and T3 in the euthyroid state. The results were divided according the TSH quartile. For all quartiles the FT3/FT4 ratio and the TSH FT3 correlation were calculated.

Results: In the study population there was a significant positive linear correlation of TSH with FT3 (R= 0.12; p0.0001), but no significant correlation with FT4.

TSH quartile	TSH (mIU/L)	FT3 (pmol/L)	FT4 (pmol/L)	FT3 to FT4 correlation	FT3/FT4 (ratio)
1st	0.33-1.86	5.85	16.34	0.263	0.36*
2nd	1.87-2.58	5.99*	16.25	0.35*	0.37*
3rd	2.59-3.55	6.07*	16.12	0.401*	0.38*
4th	3.56-7.5	6.18*	16.19	0.465*	0.397*

*p<0.05 when compared with TSH 1st quartile

Conclusion: People with higher TSH have elevated FT3 and FT3/FT4 ratio. According to studies on thyroid cell cultures TSH elevate deiodinases activity and hence increased FT3 and FT33/FT4 ratio. This is the first time this phenomenon is described in population study.

The Increase in Liver HDAC10 Induced by Food Restriction is Mediated by a Serum-Component

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[2]*Felsenstein Medical Research Center, Pediatric Endocrinology*
[3]*Endocrinology and Diabetes, Children's Medical Center of Israel*

Background: The association between children's growth and their nutritional status is well established, but the exact mechanism by which nutrition affects growth has not been completely elucidated. Using a food restriction protocol, followed by re-feeding, we have previously shown global changes in gene expression within the growth plate, suggesting epigenetic regulation of the growth processes. Indeed, we found that the level of several HDACs was significantly affected by the nutritional manipulation.

Methodology: 1. Prepubertal rats were subjected to 10 days of 40% food restriction (RES), followed by a renewal of unlimited food supply (CU) for one day; animals were sacrificed and internal organs were excised. 2. Hepatocyte cell line (Huh7) was used to study the mechanism of growth attenuation.

Results: The weight of the animals, as well as the internal organs which was significantly lower in the RES groups, rapidly increased after one day of re-feeding. To study if the effect is mediated by systemic factor, serum derived from the three groups (control (AL), RES or CU), was added to the culture medium of, Huh7 cell line, instead of the fetal calf serum. Cell viability was significantly reduced in the presence of RES serum compared to AL, while no difference was noted between AL and CU serum. The protein level of HDAC10, which was significantly increased by food restriction in the liver, was also increased when cells were incubated with RES serum.

Conclusions: Our results imply that metabolic control over liver growth is apparently mediated, at least in part, by serum components.

Activation Mechanism of p38MAPK by GnRH and PMA in Pituitary Gonadotropes

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Gonadotropin releasing hormone (GnRH) is a hypothalamic decapeptide that serves as a key regulator of the reproductive system in vertebrates and stimulates pituitary gonadotropes to synthesize and release luteinizing hormone (LH) and follicle stimulating hormone (FSH). Interaction of GnRH with its cognate receptor (GnRHR) leads to intracellular mechanism that includes activation of Mitogen-activated protein kinase (MAPK) cascades. One of the MAPKs is p38MAPK. Here we describe the role of PKC isoforms in GnRH-stimulated p38MAPK in αT3-1 and LβT2 gonadotrope cell lines. Incubation of the cells with GnRH resulted in a protracted activation of p38. By using the PKC activator, phorbol-12-myristate-13-acetate (PMA) we found that PKC is involved in the activation phase of p38 by GnRH. The gonadotrope cell lines αT3-1 and LβT2 express PKCα, βII, δ, ε, θ, η, ι/λ and ζ, that represent members of all groups of the PKC isoforms. The pan PKC isoform inhibitor, GF109203X reduced GnRH- and PMA-stimulation of p38. The use of PKCs antagonist peptide of the various PKCs has revealed that PKCα, PKCδ and PKCε mediate p38 activation by GnRH in αT3-1, while PKCα, PKCβII, PKCδ and PKCε are involved in p38MAPK activation by GnRH in LβT2 cells. Similarly, PKCα, PKCβII and PKCδ are involved in PMA activation of p38MAPK in αT3-1 cells. Furthermore, unlike the dogma that p38 is localized in the nucleus of various cells, we localized p38 to the plasma membrane. Upon activation by GnRH, we noticed blebs formation, apparent migration and relocation of p38 to the blebs. We suggest that the activated p38MAPK may be involved in gonadotropes migration, while the physiological significance of the cells migration is under investigation.

The Combination of the Dual PI(3)K/mTOR inhibitor NVP-BEZ235 with Autophagy Inhibitors is Synergistic in Suppressing Neuroendocrine Tumor Cell Viability

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David J. Gross, **Simona Glasberg**

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Background: Most patients with neuroendocrine tumors (NETs) require systemic treatment, often with limited therapeutic effect. RAD001 and Torin1 are mTOR inhibitors (mTORi) known to suppress cell proliferation in NETs, whereas the dual mTOR/PI(3)K inhibitor NVP-BEZ235 is more efficient compared to RAD001 in NET cells suppression. Cancer cells may use mTORi induced autophagy to escape the anti-proliferative effect and to prolong survival. Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) have been shown to inhibit autophagy.

Aim: To explore the effect of autophagy inhibitors alone or in combination with mTORi on NET cell proliferation.

Methods: NET cell line BON-1 was treated with NVP-BEZ235, Torin1, RAD001, HCQ and CQ alone or in combinations. Cell viability was examined by XTT method. Flow cytometry and Western blot were used to assess drug effect on cell cycle, apoptosis, PI3K/Akt/ mTOR and autophagy.

Results: NVP-BEZ235 & Torin1 significantly decreased NET cell viability compared to RAD001, whereas HCQ and CQ mildly suppressed cell viability. RAD001 in combination with HCQ or CQ did not increase the inhibitory effect of either drug given alone. Torin1 but more so NVP-BEZ235 significantly reduced cell viability, arrested cells in G0/G1, and induced a higher degree of apoptosis, mainly in combination with HCQ or CQ. The combination of NVP-BEZ235 and autophagy inhibitors significantly increased the accumulation of LC3-II, a marker for autophagy inhibition.

Conclusion: The combination of the dual PI(3)K/mTOR inhibitor NVP-BEZ235 with autophagy inhibitors seems promising for the inhibition of NET cell proliferation.

Identification of BRCA1 as a Biomarker for IGF-IR Targeted Therapy in Breast Cancer

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Background: The insulin-like growth factor 1 (IGF-I) belongs to a family of mitogenic polypeptides with significant roles in growth and differentiation. IGF-I receptor (IGF-IR) plays a key role in tumor formation and is overexpressed in most of the tumors. Therefore, the IGF-IR emerged recently as a promising therapeutic target. Previously, our lab has shown that BRCA1 reduces the expression of endogenous IGF-IR and the promoter activity, suggesting that the IGF-IR gene is a downstream target of BRCA1. The main objective of my thesis is to examine whether the efficacy of IGF-IR-directed therapies depends on the BRCA1 status. We postulate that the BRCA1 status should predict responsiveness to IGF-IR inhibitors (MK-0646 antibody), rendering BRCA1-defective cancers more sensitive to the treatment.

Methods: To evaluate this hypothesis, ereas shRNA will be used to reduce BRCA1 expression in wild-type BRCA1 BRCA1-null breast cancer cells will be transiently transfected with a wild-type BRCA1 whcells. The cells will be treated with MK-0646 antibody, and its effectiveness will be tested in in-vitro and in-vivo models.

Results: Results of preliminary studies seem to corroborate our hypothesis suggesting that MK-0646 treatment might be more effective in mutant BRCA1- than in wild-type BRCA1-expressing breast cancers due to a higher basal IGF-IR level. These studies will be complemented by cell signaling analyses, micro-array assays and in vivo experiments.

Conclusions: Taken together, this study will provide, for the first time, a correlation between BRCA1 status and the capacity of MK-0646 to target the IGF-IR and a solid basis for prediction of MK-0646 treatment effectiveness.

Vascular Endothelial Growth Factor (VEGF) Levels in Short, GH Treated Children: A Distinct Pattern of VEGF-C in Noonan Syndrome

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[3]*Sackler Faculty of Medicine, Tel Aviv University*
[4]*Department of Molecular Genetics, Weizmann Institute of Science*

Context: Noonan syndrome (NS) is characterized by short stature and elevated risk of lymphedema. The mechanisms underlying lymphedema may be failed lymphangiogenesis mediated primarily by vascular endothelial growth factor (VEGF).

Objective: To assess the effect of growth hormone (GH) treatment on plasma insulin-like growth factor (IGF)-1, VEGF-A and VEGF-C levels in patients with NS as compared to short GH-sufficient children.

Design: Retrospective, comparative.

Setting: Endocrinology department of a tertiary pediatric medical center.

Patients & Methods: Plasma IGF-1, VEGF-A and VEGF-C levels were measured before and during GH treatment in 6 patients with NS and 18 age-matched short subjects (Turner, idiopathic short stature and small for gestational age).

Main outcome measures: Changes in plasma VEGF and IGF-1evels.

Results: Baseline IGF-1 SDS levels were slightly lower in NS patients compared with controls; IGF-1 response to GH therapy was markedly lower in NS patients compared with controls ($p=0.017$). Mean baseline VEGF-A levels were similar in NS patients and controls whilst mean baseline VEGF-C levels were significantly lower in the NS group as compared with controls ($p=0.022$). Plasma VEGF-A and VEGF-C levels did not significantly change during GH treatment in the study cohort. No correlation was found between VEGF-C levels and levels of IGF-1, VEGF-A and auxological parameters, either before or during GH administration.

Conclusion: Children with NS have a distinct growth factor profile including low basal VEGF-C and flattened IGF-1 response to GH. Further studies are needed to confirm our findings and to elucidate the interaction between VEGF-C levels and lymphedema.

Severity of the Endocrine Condition at First Referral in Pediatric Patients is Associated with Gender, Ethnicity and Socio-economic Status

Inbar Safra[2], Shlomit Shalitin[1,2], Ariel Tenenbaum[1], Eran Mel[1], Alon Farfel[1], Rachel Frumkin Ben-David[1], Nitzan Dror[1], Tal Oron[1], Moshe Phillip[1,2], Yael Lebenthal[1,2]

[1]*The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University*

Background: Studies from other countries have shown an association between the severity of endocrine condition and socio-demographic parameters. To date, no large-scale studies have been published in Israel.

Objective: To assess the severity of the endocrine condition at time of first referral in association with socio-economic status (SES), gender and ethnicity.

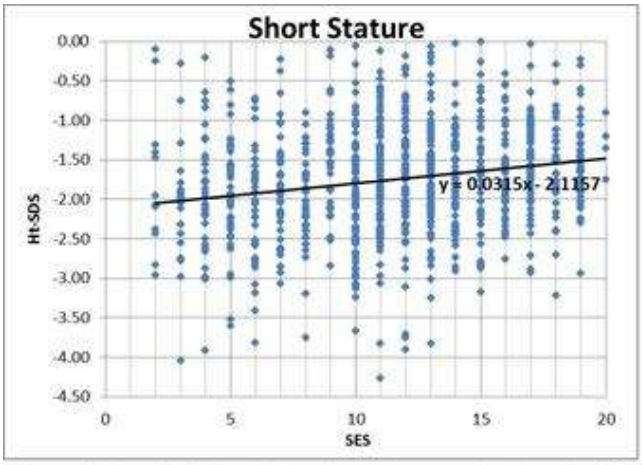
Design: Retrospective chart review. Setting: Endocrinology department at Schneider Children's Medical Center of Israel

Patients & Methods: 4528 new patients referred during 2011 & 2012 were screened for eligibility. Included in the study were 1468 patients referred for growth and weight disorders. Information collected included referral diagnosis as well as anthropometric and demographic data.

Main outcome measures: Height SDS and BMI SDS.

Results: In our study cohort growth disorders represented 79.6% of referrals (94.7% suspected short stature); 45.9% were defined as having a true endocrine condition (±2 SDS). A significant correlation was found between lower SES and more severe short stature and overweight (R=0.20 and R=-0.20 respectively, P0.001). Girls had lower Ht-SDS (-1.83±0.70 vs. -1.72±0.69, P0.05), and boys had higher BMI-SDS (2.28±0.81 vs. 2.09±0.61, P0.05). Ethiopian-Jews had lower Ht-SDS compared to non-Ethiopian-Jews (-2.10±0.57 vs. -1.75±0.68, P0.05). No significant differences were found between other ethnic groups.

Conclusions: Our findings suggest that lower SES, gender and ethnicity were important factors affecting referrals and therefore severity at presentation.



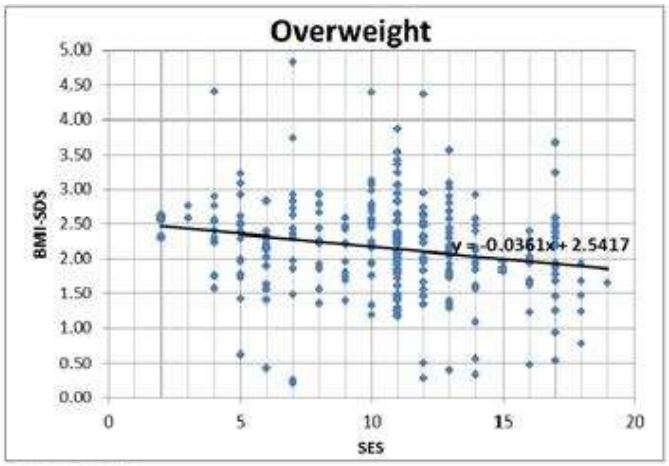
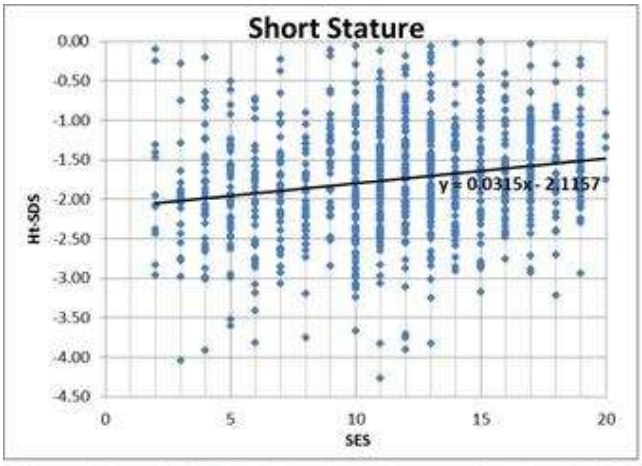


Figure 2a Severity of short stature by socio-economic status. N= 939, R=0.198, P<0.001.
Figure 2b Severity of overweight by socio-economic status. N=284, R = (-0.200), P<0.001



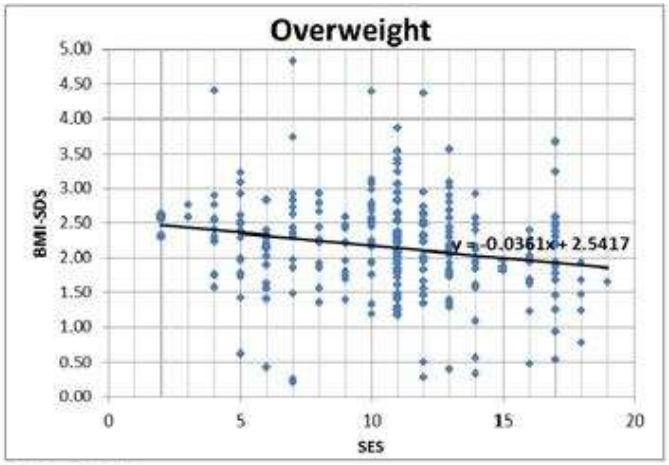


Figure 2a Severity of short stature by socio-economic status. N= 939, R=0.198, P<0.001.
Figure 2b Severity of overweight by socio-economic status. N=284, R = (-0.200), P<0.001

Compliance, Persistence and Preferences towards Osteoporosis Treatment among Post-menopausal Israeli Women during Active Therapy or Drug Holiday

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[2]*Medical Management Department, Meir Medical Center, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University*
[3]*Division of Clinical Pharmacy, School of Pharmacy, The Hebrew University of Jerusalem*
[4]*Bone Health Service, Endocrine Unit, Department of Medicine E, Meir Medical Center, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University*

Background: Osteoporosis treatments reduce the risk of fractures, but compliance after one year is only about 50%. Low compliance increases the risk of fractures.

Objectives: Determine compliance and persistence with therapy and attitudes regarding resuming treatment among patients of a metabolic bone clinic on active therapy or drug holiday.

Methods: Compliance was assessed by medication possession ratio (MPR), representing the number of doses dispensed in relation to prescribed. Persistence was defined as treatment continuation without 30-days between refills. Data were collected by personal interviews.

Results: Of 100 patients (70.2±7.7 years-old), 55% were receiving treatment; 60% an oral medication, mostly bisphosphonates. MPR was ≥80% in 82% and 50% in 13%. MPR was 100% for zoledronate, denosumab and raloxifene, and 92%, 89% and 71% for teriparatide, oral bisphosphonates and strontium ranelate, respectively. Of 27 patients on bisphosphonates, 63% persisted with treatment. Of 40 patients on a drug holiday, 20% expressed concern about resuming treatment, while 65% expressed confidence in their physician's treatment choice.

Conclusions: Compliance among our patients was higher than reported. MPR for oral bisphosphonates and percutaneous treatments were high; lower for strontium ranelate. High persistence and compliance might be specific to patients from a dedicated bone diseases clinic. This study provides new information about the attitudes of osteoporosis patients on a scheduled drug holiday. Most were not concerned about resuming treatment and did not have a preferred medication. These results indicate that a trusting relationship between patient and doctor seems to be an important factor in medication compliance.

Urinary Deoxypyridinoline Cross-link (uDPD) in the Management of Osteoporotic Women on Long-term Bisphosphonates Treatment

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In recent years there is increased awareness regarding adverse effects associated with the use of anti-resorptive agents, particularly bisphosphonates, in the treatment of osteoporosis. Prolonged treatment with oral bisphosphonates, typically characterized by low bioavailability, may coincide with physiological changes in the intestinal tract that may further affect their absorption following oral administration. The current data provides some insight on uDPD, a marker of bone resorption, in patients on long-term bisphosphonates treatment, and its utilization in the management of postmenopausal osteoporotic women.

Methods: Unselected, retrospectively collected data from records of osteoporotic patients on oral bisphosphonates attended by the author in the endocrine clinic.

Results: There were a total of 195 women of a mean age of 64 years. The vast majority received alendronate. The mean duration of bisphosphonates treatment was 6.7 years. We observed a tendency towards increased uDPD with advancing age and a significant correlation between uDPD and duration of bisphosphonates treatment. In approximately 3% of the patients uDPD was below the reference range for premenopausal women, and in approximately 20% uDPD exceeded the upper limit of the range.

Conclusions: A considerable proportion of women on oral bisphosphonate treatment present with uDPD elevated uDPD reflecting sub-optimal control by oral bisphosphonate treatment. This could be attributed to either poor compliance, or to physiological, age-related, changes in gastrointestinal properties further affecting the poor enteral absorption of oral bisphosphonates. The present results imply that uDPD seems to be a useful tool in the management of osteoporotic women on oral bisphosphonates.

The Effect of Casein and Lactalbumin on Bone Microarchitecture during Nutritional-induced Catch up Growth

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Background: Malnutrition inhibits longitudinal growth, while re-feeding induces compensatory catch up (CU) growth. In most cases it brings the child back to its original growth curve but in many cases permanent growth deficit remains.

Objective: The objective of the study was to study if re-feeding with milk proteins enriched diet can improve CU growth, and to investigate the effect on bone length and quality in an animal model using micro-Computer Tomography (micro-CT).

Methods: Young male Sprague Dawley rats were subjected to 36 days of 40% food restriction (RES, n=7), followed by 24 days of refeeding with chow containing casein (Cas, n=7) or lactalbumin (Lact, n=7) as the sole source of protein. Rats fed ad libitum served as control (AL, n=5).

Results: the average body weight of casein and lactalbumin refed rats was significantly lower compared to the AL group. In spite of similar body weight and humerus length between Cas and Lact groups; the micro-CT analysis demonstartes significant differences in bone morphology between the two groups. Rats from the Cas group had significantly thicker cortex (Ct.Th (p0.05)). In addition, they had higher trabecular bone volume (BV/TV (p0.05)), trabecular number (Tb.N (p0.05)), trabecular thickness (Tb.Th (p0.05) and connectivity (Conn.D (p0.05)), with smaller trabecular spacing (Tb.Sp (p0.05) compared to the Lact group. In addition, Cas group had greater Bone mineral density (BMD) and bone meniral content (BMC) compared to the Lact group (p0.

Conclusion: Micro-CT analysis showed that cortical and trabecular bone architecture significantly improved with casein enriched diet compared to lactalbumin diet.

Carnosic Acid Decreases the Expression of 24-Hydroxylase (CYP24A1) Induced by 1,25-Dihydroxyvitamin D3 in Human Acute Myeloid Leukemia (AML) Cell Lines

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CYP24A1 is responsible for the catabolism of active forms of vitamin D, such as 1,25(OH)2D3, and is activated by these agents as a negative feedback. Overexpression of CYP24A1 in cancer correlates with poor prognosis; however, studies in knock-out mice show that an absence of this gene leads to acute hypercalcemia and hypervitaminosis D. A low-toxic adjuvant that can reduce the expression and/or activation of CYP24A1 may contribute to the treatment of different types of cancer. The aim of this study was to assess the effect of carnosic acid (CA), a polyphenol extracted from the rosemary plant, on the expression of CYP24A1, and the mechanisms underlying this effect. By transfecting U937 cells with a CYP24A1 promoter-luciferase reporter construct we demonstrated that CA strongly inhibits 1,25(OH)2D3-stimulated promoter activation in a dose-dependent manner. Furthermore, in both U937 and HL60 cells, CA decreased 1,25(OH)2D3-induced CYP24A1 mRNA expression. Mutations in VDRE1 or VDRE2 sequence of the promoter construct did not abolish the inhibitory effect of CA. However, trichostatin A, a histone deacetylase inhibitor, partially prevented the effect of CA on the promoter bearing inactive VDRE2. In addition, overexpression of the transcription factor Nrf2, which is known to be activated by CA, resulted in reduced CYP24 promoter activation by 1,25(OH)2D3, while dominant-negative Nrf2 had an opposite effect. Collectively, CA can suppress 1,25(OH)2D3-induced CYP24A1 expression in AML cells, which may be mediated, at least in part, by Nrf2 and histone deacetylases. This may stabilize local 1,25(OH)2D3 levels, thereby enhancing its antileukemic activity. (Supported by the Israel Science Foundation grant 635/11).

Safety of Zoledronic Acid in Post Menopausal Women with Osteoporosis: A Single Center Observational One-year Study

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In clinical trials treatment with Zoledronic acid (ZOL) was reported to induce acute phase reaction in about 15% of patients after the first infusion.

This study was aimed to evaluate the incidence of adverse events (AE) in the regular clinical setting.

Patients and Methods: 215 consecutive patients received IV ZOL 5 mg, of them 52 patients had repeated infusion of ZOL. AE's were reported by patients using a detailed form during ten days after the infusion.

Results: Women aged 69.7±9.59,(45-100) were included in the study. 151 (70%) patients were previously treated with: Alendronate 65 pts (43 %); Raloxifene 9 (5.96%); Risedronate -31(20.5%); Teriparatide 23(15.2%); Livial-1 (0.7%); calcium supplements133 (61.9%); Vitamin D 147 (68%). Any AE was reported in 136(63.3%) and 32(61.5%) patients: fever 69 (50.7%) and 10 (31.3%), p=0.024;bone /joints pain / headache 129 (94.8%) and 0, p0.0001; weakness 109 (80.1%) 20 (62.5%), p=0.05; muscles pain 106 (77.9%) and 10 (31.3%), p=0.04; uveitis 2 (1.47%) and 0 after the first and second dose respectively.

AEs duration was 2-5 days with no correlation to prior treatments. Previous fractures were reported in 114 (53%) patients. There were 5 (2.3%) new fractures: 3 hip; 2 ramus pubis.

Conclusion: Incidence of the acute phase reaction in the study was higher than previously reported with a significant decrease after the second dose.

Patients with Atypical Femoral Fractures: Characteristics, Anabolic Treatment and Long Term Follow up

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Background: Atypical fractures (AF) of femoral shaft have distinct radiologic features and are probably related to prolonged bisphosphonate (BP) exposure. They are currently considered to be insufficiency fractures occurring in osteoporotic bone. After initial damage, the repair process calls for accelerated remodeling, but the later is prevented by BP accumulation on the remodeling site. Thus, the fracture expands instead of healing. The management is not postulated, but anabolic treatment makes sense and a few case reports regarding teriparatide use have been published. Long term follow up data is lacking. The aim of this report was to summarize our experience with AF patients – clinical characteristics, treatment and outcomes.

Patients: Seven female patients were followed prospectively since 2008. The median age was 66. All of them were BP exposed, and mean treatment duration was 8 years. Two patients were steroid treated. The majority (57%) sustained osteoporotic fractures prior to the index event. None smoked. Their vitamin D levels were 20 ng/ml, in all. Bone density prior to AF was in the osteoporotic range: lumbar spine T-score minus 3.48 + 1.1 and femoral neck minus 2.9 + 1.

Results: Three patients presented with complete shaft fracture, four had lateral cortex incomplete fractures (one of those bilateral). Bisphosphonate was discontinued in all patients and six (85 %) were offered teriparatide (TPT) treatment. Two patients with lateral cortex incomplete fractures progressed to a complete fracture while on TPT. Median follow up was 48 month. Hip bone density was significantly improved. None sustained another fracture.

Conclusions: AF occurred in high risk patients. In our small cohort, TPT failed to prevent incomplete fracture progression in half of the participants. Anabolic treatment was effective in terms of bone density improvement.

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