ISRAEL ENDOCRINE SOCIETY

IES

האגודה הישראלית לאנדוקרינולוגיה

The 42nd IES Annual Meeting 2013
Detailed Program

April 9 -10, 2013
Leonardo City Tower Hotel
Ramat-Gan

Scientific Program and Abstracts

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צאיתים/ות יקרים/ות

ברוכים הבאים לכינוס ה- 42 של האגודה הישראלית לאנדוקרינולוגיה. בימים אלה מלאה שנה לפעילות הועד החדש. שנה זו עמדה בסימן המשך הפעילות המבורכת שבוצעה תחת שרביט הועד הקודם - תוך התחדשות ופתיחת ערוצי פעילות נוספים.

בפני הועד הנוכחי ניצבים אתגרים רבים. ההתקדמות המדעית בתחום מחייבת שיתוף פעולה הדדי ופורה בין העוסקים/ות במחקר בסיסי וקליני לרופאים/ות המטפלים/ות בחולים. היזון חוזר מרמת המעבדה למיטת החולה, יאפשר לצמצם את הפער הגדל ומתרחב בין הידע המדעי הבסיסי בכלל ובאנדוקרינולוגיה בפרט למידת יישומו הקליני. לאגודה האנדוקרינית תפקיד קריטי לעידוד המחקר הבסיסי והקליני, לבניית קוים מנחים קליניים עדכניים, ולהכנסת תרופות חדשות לסל הבריאות. במקביל חשוב לנו לחזק את מעמד האנדוקרינולוגיה במערכת הקלינית, להגדיר את התקינה במרכזים הרפואיים ובקהילה ולמשוך מתמחים צעירים שישלבו עבודה קלינית עם מחקר.

בהתאם גם השנה נמשך שיתוף הפעולה הייחודי בין החברים העוסקים במדע הבסיסי לבין הקלינאים. שיתוף פעולה פורה ומפרה זה הינו יוצא דופן בנוף האיגודים המקצועיים של הר"י. לכן, פעלנו ונמשיך גם בעתיד להעניק מלגות למחקרי היתכנות בנושאי סוכרת, מחלות עצם מטבוליות, ונוירואנדוקרינולוגיה לחוקרים/ות צעירים/ות ולהקצות מלגות נסיעה לחברי/ות האגודה המציגים עבודות בכינוסים מדעיים בחו"ל. בשנה הקרובה אנו מתכוונים להעמיק את שיתוף הפעולה וליזום ימי עיון נושאיים המתאימים לכל – מהסטודנט ועד לרופא הבכיר.

המשכנו בפעילות הכנסים הדו שנתית. כנס הסתיו באילת התקיים לפי מתכונת השנים הקודמות ונחל הצלחה מרובה. הכנס שנושאו: Novel Drug Therapies In Endocrine Disorders נערך בשיתוף ובתמיכת חברות התרופות ותרם להעמקת הקשר עם התעשייה התומכת בפעילות מחקרית ובכנסים המדעיים. בכנס החורף וגם בכנס הנוכחי מיקדנו פעילות בתחום הסכרת והמטבוליזם וזאת לאור העיסוק הקליני והמחקרי של רבים מחברינו בתחומים חשובים אלה והתרומה הייחודית שלהם בארץ ובעולם.

הכנס השנתי הנוכחי משלב מרצים אורחים ממיטב האנדוקרינולוגים בעולם יחד עם חוקרים וקלינאים מעולים מארצנו. הנושאים בהם מתמקד בכנס – החל מסכרת ומטבוליזם, בלוטת התריס, סטרואידוגנזיס, מעבר הטיפול במחלות אנדוקריניות מילדות לבגרות ועד תאי גזע ומנגנונים מולקולריים – הינם מאבני היסוד של האנדוקרינולוגיה המודרנית. הכנס השנה הינו רחב יריעה, יתקיימו בו 3 הרצאות מליאה, 7 סימפוזיונים, 5 מושבי הרצאות של חברי האגודה, 4 מושבי "פגוש את המומחה" וסיור פוסטרים מודרך. שפת הכנס הרשמית הינה עברית, אך עקב ריבוי המושבים עם אורחים מחו"ל חלק מההרצאות תתקיימנה באנגלית. תודתנו נתונה לכל החברים ששלחו תקצירים לכנס ואנו מאחלים הצלחה למצטיינים ומקוים להשתתפות ערה ולכנס פורה.

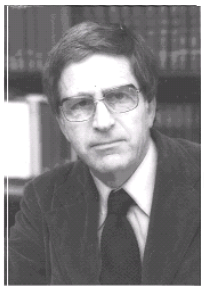
כבכל שנה – נעניק גם השנה את פרסי האגודה על שם פרופ' הנס יוחנן לינדנר ז"ל ופרופ' ישראל חוברס ז"ל ופרסים לתקצירים ולפוסטרים המצטיינים. ננצל את מסגרת הכנס להודות לחברינו באגודה הפורשים לגמלאות, ונכבד את אלו שהלכו לעולמם.

ולסיכום – שנת הפעילות הראשונה שלנו כוועד הייתה רבת מעש. אנו גאים מאד בכל הישגי האגודה מאז קיומה - בתרומה המדעית של חברינו ובהצלחה לשלב מדע בסיסי וקליני. בשנה הבאה מקוים להרחיב את הפעילות המדעית, להוסיף ימי עיון, ולהגדיל את היקף האגודה ומספר חבריה. בסימן ירוק מפורסם השנה ספר התקצירים באתר האגודה ומופץ לחברים באופן אלקטרוני, עזרו לנו להתחשב בסביבה.

תודה מקרב לב לכל החברים/ות, לחברות התומכות ולמערכת הארגונית אשר מסייעים לנו בעשייה ומאחלים לכולנו כנס מוצלח והמשך שיתוף פעולה פורה.

ועד האגודה

פרופ' הנס יוחנן לינדנר ז"ל – מילים לזכרו



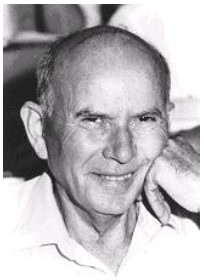
פרופ' הנס יוחנן לינדנר נולד בשנת 1922 בגרמניה ועלה ארצה עם הוריו בשנת 1936. לאחר מלחמת השחרור הוא למד רפואה וטרינארית בסידני (אוסטרליה) וסיים בהצטיינות.
את לימודיו לתואר .Ph.D הוא השלים באוניברסיטת קיימברידג' שבאנגליה. עם תום לימודיו, חזר לינדנר לאוסטרליה, התמנה כחוקר בכיר ב- Commonwealth Scientific 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' לינדנר היה פעיל גם בארגונים בינל"א: חבר בועדות של WHO, של מכון מקס-פלאנק בגרמניה, של INSERM בצרפת, של ארגונים אנדוקריניים בינל"א וב-Editorial Board של עיתונים מדעיים. הוענקו לו תארי כבוד במס' אוניברסיטאות בעולם.
בשנת 1979 הוענק לו פרס ישראל במדעי החיים והוא נבחר כחבר באקדמיה הישראלית למדעים. בשנת 1982 הוענקו לו פרס רוטשילד בביולוגיה וכמו כן, פרס Axel- Munthe בשטח הביולוגיה של הפוריות. פרופ' הנס יוחנן לינדנר נפטר בשנת 1982 עקב מחלה קשה.
כראש המחלקה לחקר ההורמונים הכשיר פרופ' לינדנר דורות של חוקרים בתחום האנדוקרינולוגיה.
הפרס ע"ש פרופ' לינדנר הוא הפרס היוקרתי ביותר של האגודה הישראלית לאנדוקרינולגיה. הפרס ניתן לחוקר/ת, מתחת לגיל 50, עבור הישגים מדעיים בתחום האנדוקרינולוגיה במהלך חמש השנים האחרונות.

זוכי פרס לינדנר

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

יובל דור - 2013

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 אזור 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 באוניברסיטה של פנסילבניה, שם עבד בשיתוף עם פרופ' McCann שעבודתו הקנתה לו מעמד של חלוץ במחקר הנוירואנדוקריני בתחום הקשר בין ההיפותלמוס והורמוני יותרת המוח, ובעיקר בגילוי ובאפיון של הפקטור ההיפותלמי המזרז את הפרשת הגונדוטרופינים 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 לאנדוקרינולוגיה ניסויית במסגרת מחלקת עצבים. פרופ' חוברס וקבוצתו עסקו בחקר מנגנונים עצביים ואנדוקריניים הקשורים בויסות חום הגוף ובתפקיד מערכת העצבים המרכזית בויסות הפעלת הורמוני הדחק. כמו כן, עסקה מעבדתו בחקר יחסי הגומלין בין ההיפותלמוס האינסולין ורמת הגלוקוז בדם. מחקריו של פרופ' חוברס הקנו לו שם בינלאומי בתחום הנוירואנדוקרינולוגיה. הוא הוזמן להציג את מחקריו בפני כנסים בינלאומיים ושהה כמדען אורח באוניברסיטאות ובמכוני מחקר מהחשובים בעולם. לצד עיסוקו ברפואה, במחקר ובהוראה, מצא פרופ' חוברס זמן לתת שירותים רפואיים ללא תמורה לאוכלוסיה מעוטת יכולת בירושלים.

ב-1975 מונה פרופ' חוברס כמנהל המח' האנדוקרינית ומכון המחקר ע"ש רוגוף בביה"ח בילינסון. עם זאת, אהבתו לירושלים ולביתו בבית-זית ושאיפתו לעסוק ברפואה פנימית על כל היבטיה, הביאו אותו לקבל את הצעת ביה"ח "ביקור חולים" לנהל את המח' הפנימית. על אף הקשיים הרבים שבהם היה נתון ביה"ח, ובמיוחד המח' הפנימית, הצליח פרופ' חוברס, בזמן קצר יחסית, לארגן צוות רופאים ועובדים ולשנות כליל את פני המחלקה. ביוזמתו עבר ביה"ח שינויים ניכרים לקראת הפיכתו לבית-חולים מודרני ואוניברסיטאי. במסגרת שיקום המחלקה, הקדיש פרופ' חוברס תשומת לב רבה לשטח האנדוקרינולוגיה ובמיוחד לנושא הסוכרת. הוא הקים יחידת סוכרת עם ציוד מודרני וייחודי להדרכה, אבחון, טיפול ומחקר קליני.

במקביל לעבודתו בביה"ח "ביקור חולים", מונה פרופ' חוברס כמנהל השירות האנדוקריני של קופ"ח הכללית בירושלים. במסגרת זו הוא ארגן וניהל את מרפאת הסוכרת של קופ"ח בפרוז'ינין אשר סיפקה את שירותיה לאלפי חולי סוכרת במחוז י-ם.

פרופ' חוברס הקים וחינך דור של רופאים וחוקרים העוסקים ברפואה פנימית, אנדוקרינולוגיה וסוכרת. הוא הדגיש תמיד את חשיבות הגישה החמה לחולה ובמיוחד לחולה הבודד והקשה.

פרופ' חוברס, שהיה מותיקי האגודה הישראלית לאנדוקרינולוגיה, נפטר באופן פתאומי ב-3.2.89. לאחר מותו, יסדה משפחתו פרס לזכרו לשם קידום המחקר האנדוקריני בישראל. הפרס מוענק לחוקר צעיר, מתחת לגיל 45 עבור עבודה בתחום האנדוקרינולוגיה שפורסמה בשנה האחרונה (או עומדת להתפרסם).

זוכי פרס חוברס

1992- דניאל מלול
1993- טלי נוה-מני
1994- ליאורה שוקובסקי
1995- איריס קרן-טל
1996- קרן פז
1997- פואד פארס
1998- אסף רודיך
1999- סיגל כורם
2000- אפרת וורטהיימר
2001- אלון חן
2002- רינה המי
2003- יעל קלמה
2004- שלומי לזר
2006- אמיר תירוש
2007- נועה שר וערן גרשון
2008- עירית מיבר-לוי
2009- עידו וולף
2010- מוריר חמאיסי
2011- רעות אשואל
2012 – יעל קופרמן

יונית מרקוס - 2013

IES 2013 Annual Meeting – Detailed Program

April 9 – 10, 2013, Leonardo City Tower Hotel, Tel Aviv

Updated April 3rd 2013

Tuesday, April 9th 2013			
7:30-8:00	Registration		
8:00-9:45	**Short oral presentations (3 parallel sessions)**		
Diabetes, Obesity & Metabolism- Bareket Hall Chairs: Benjamin Glaser and Hannah Kanety	**Thyroid & Adrenal- Shoham Hall** Chairs: Zaki Kraiem and Pnina Rotman	**Bone, Vitamin D and Calcium Metabolism- Coral Hall** Chairs: Dov Tiosano and Liana Tripto	
9:45-10:15	Coffee break		
10:15-10:25	**Opening remarks: Eddy Karnieli and Alon Chen- Bareket Hall**		
10:25- 11:15	**Plenary Lecture 1 - Chair: Alon Chen and Yoav Sharoni- Bareket Hall** **Walter Miller, "New aspects of androgen biosynthesis"**		
11:15-12:30	Guided poster session		
12:30-13:30	Lunch		
13:30-14:30	**Plenary lecture 2 - Chairs: Eddy Karnieli and Derek Leroith- Bareket Hall** **Gerald Shulman, "Cellular mechanisms of insulin resistance: Implications for obesity, lipodystrophy, type 2 diabetes and the metabolic syndrome"**		
14:30-16:00	**Symposiums (2 parallel sessions):**		
Cholesterol trafficking and cleavage: mechanisms and clinical implications **Bareket Hall** Chairs: Yossi Orly and Eli Hershkovitz		**Transition in Endocrine Care** **Madrid-Milano Hall-** ***Sponsored by Novo Nordisk*** Chairs: Orit Pinhas-Hamiel and Nehama Zuckerman-Levin	
Walter Miller, "Pathogenesis and Physiology of Congenital Lipoid Adrenal Hyperplasia"		**Alan Rogol**, "Transition from pediatric-based care to adult-based care: The example of T1DM and growth hormone deficiency	
Eli Hershkovitz, "Side Chain Cleavage enzyme defects-varied and unexpected phenotypes"		**Ohad Cohen and Yael Levy-Shraga**, "Transition Clinic at Sheba Medical Center: principles and results"	
Moshe Gavish "Biological relevance of TSPO- steroid interactions"		Roundtable discussion: "Is a child a small adult?" Moderator: Amnon Zung	
Yossi Orly, "StAR impact on mitochondria: remodeling the organelle protein quality control machinery"			
16:00-16:20 Coffee break			
16:20-17:20	**Meet the Professor / Expert (2 parallel sessions):**		
Emerging role for microRNA in endocrine tissues – Madrid-Milano Hall		**Year in Pituitary- Tokyo Hall**	
Eran Hornstein, "Regulation of beta-cell mass and identity by microRNAs"		**Yona Greenman**, "The year in Pituitary: summary and review of the latest advancements in the field"	
Michael Walker, "Regulating the regulators: transcriptional control of miRNA genes"			

IES 2013 Annual Meeting – Detailed Program

April 9 – 10, 2013, Leonardo City Tower Hotel, Tel Aviv

Wednesday, April 10th 2013			
7:30-8:00	Registration		
8:00-9:45	**Short oral presentations (2 parallel sessions) and one Symposium**		
Pregnancy and endocrinology- Chairs: Ilan Shimon and Moshe Hod- Bareket Hall		**IGFs and Cancer -** Chairs: Haim Werner and Philippa Melamed **– Shoham Hall**	**Reproduction and Puberty** Chair: Venessa Rouach and Zeev Blumenfeld - **Coral Hall**
Moshe Zloczower, Basal insulins in pregnancy - old vs. new players			
Yoel Toledano, Management of Pituitary Tumors in Pregnancy			
Yariv Yogev, Bariatric Surgery: Impact on Pregnancy			
9:45-10:15	Coffee break		
10:15-11:45	**Symposiums (2 parallel sessions):**		
Stem cells in endocrine research - Chairs: Rina Meidan and Karen Tordjman**- Bareket Hall**		**Osteoporosis:** Chairs: Yair Liel and Elena Segal **Madrid-Milano Hall**	
Shimon Efrat, "Ex-vivo generation of insulin-producing cells for beta-cell replacement in diabetes"		**Jaron Rabinovici**, "Treatment of the early post-menopausal woman: update on HRT and SERM therapies"	
Sarah Ferber, "Autologous cell replacement therapy for diabetes-by adult cell reprogramming"		**Sofia Ish-Shalom**, "The use of bone turnover markers in the treatment of osteoporosis"	
Lilach Gilboa, "Hormonal regulation of germ line stem cell establishment"		**Iris Vered,** "Bisphosphonates for osteoporosis: issues of timing, time limits and alternatives"	
		Rivka Dresner-Pollack, "Sweet bones- osteoporosis in diabetic patients"	
11:45-13:00	**Prizes session and IES members assembly meeting- Bareket Hall**		
13:00-14:00	Lunch		
14:00-15:00	**Plenary lecture 3- Chair: Carlos Benbassat- Bareket Hall** **Richard Kloos, "Differentiated thyroid cancer: the approach to the patient with persistent disease"**		
15:00-16:30	Symposiums (2 parallel sessions):		
New Developments in Thyroid Cancer **Bareket Hall- *Sponsored by Genzyme*** Chairs: Eyal Robenshtok and Anat Yaffe		**Emerging translation aspects in diabetes and obesity research** **Madrid-Milano Hall** Chairs: Avi Karasik and Naftali Stern	
Richard Kloos, "Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate FNA Cytology"		**Yehiel Zick**, "Novel targets of cytokine-induced beta cell death"	
Gideon Bachar, "Robotic transaxillary thyroidectomy: indications, technique and patients outcomes"		**Hannah Kanety**, "Post-transcriptional gene regulation by microRNAs and RNA-binding proteins in obesity and diabetes"	
Ohad Cohen, "Radioactive iodine therapy: When, how and how much?"		**Derek Leroith**, " Diabetes and cancer risk: the roles of insulin and cholesterol"	
Aharon Popovitzer, "The role of modern biological treatments in advanced thyroid cancer"			
16:30-16:45	Coffee break		
16:45-17:45	**Meet the Professor Madrid Milano Hall**	**Meet the Professor New York Hall**	
Richard Kloos, "Treatment of well differentiated thyroid cancer: open discussion on an index case"		**Alan Rogol**, "Doping in sport with endocrine system active agents: An issue of Olympic proportions"	

Plenary Lectures:

1. "New Aspects of Androgen Biosynthesis"

Walter L. Miller, ***University of California San Francisco, CA USA***

The modern study of steroidogenesis has moved from studies of steroid chemistry to the genes, enzymes and pathways of steroidogenesis. Species differences have both confounded and enlightened this study. The production of all sex steroids requires P450c17 (encoded by *CYP17A1*), which first catalyzes 17α-hydroxylase activity (needed for cortisol production) and then may, or may not catalyze 17,20 lyase activity, needed sex steroid production. Studies in rodents and ungulates indicated that P450c17 catalyzes both activities with either Δ5 or Δ4 substrates, but our detailed biochemical studies showed that human P450c17 catalyzes the Δ4 reaction 17OHP→Androstenedione with only ~2% of the activity of the Δ5 reaction 17OH-pregnenolone→DHEA, so that essentially all human sex steroids are produced by the Δ5 pathway, indicating that 17OHP is a 'dead-end' steroid. The 17,20 lyase reaction is post-translationally regulated by three factors increasing the efficiency of electron transfer from NADPH: 1) a high molar ratio of P450 oxidoreductase (POR) to P450c17; 2) allosteric action of cytochrome b5 to improve the POR:P450c17 interaction; 3) Ser/Thr phosphorylation of P450c17. Accordingly, '17,20 Lyase Deficiency' is a syndrome that can be caused by mutations in P450c17, POR or b5. Studies by others in a marsupial, the Tammar Wallaby, have revealed a "backdoor pathway" of androgen production by which dihydrotestosterone (DHT) is produced from 17OHP without the intermediacy of DHEA, androstenedione or testosterone; this pathway is crucially dependent on unidentified enzymes catalyzing both reductive and oxidative 3αHSD activities. Re-examination of the index family with "17,20 desmolase deficiency" reported by Zachmann in 1972 identified lesions in the 3αHSD enzymes AKR1C2 and AKR1C4; a second family had AKR1C2 mutations alone; in vitro assays showed lost activities; RT-PCR of fetal tissues showed appropriate tissue expression. Human male sexual development is typically described as requiring fetal testicular testosterone converted to DHT by 5α-reductase in fetal genital skin. Our study shows that BOTH this classic pathway and the backdoor pathway of fetal testicular DHT synthesis are needed for normal human male sexual development. The discovery of a human androgenic pathway from 17OHP dramatically alters conventional views about mechanisms of androgenization in congenital adrenal hyperplasia and other hyperandrogenic disorders.

2. "Cellular Mechanisms of Insulin Resistance - Implications for Obesity, Lipodystrophy, Type 2 Diabetes and the Metabolic Syndrome"

Gerald I. Shulman *Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT USA*

Insulin resistance is a major factor in the pathogenesis of type 2 diabetes and the metabolic syndrome. In this lecture I will discuss recent nuclear magnetic resonance studies that have implicated ectopic lipid deposition in liver and skeletal muscle as a causal and unifying factor in the pathogenesis of insulin resistance associated with obesity, lipodystrophy, type 2 diabetes and the metabolic syndrome. I will also present results from recent human studies demonstrating an important role of intracellular diacylglycerol, as the molecular trigger for lipid-induced insulin resistance in liver through its activation of protein kinase Cε and in muscle through its activation of protein kinase Cθ, which both result in reductions in proximal insulin signaling.

3. "Differentiated Thyroid Cancer: the Approach to the Patient with Persistent Disease"

R. Richard, T Kloos, *Veracyte Inc. San Francisco, CA USA*

Symposiums

Symposium: "Cholesterol Trafficking and Cleavage - Mechanisms and Clinical Implications"

1. "Pathogenesis and Physiology of Congenital Lipoid Adrenal Hyperplasia"

Walter L. Miller, *University of California San Francisco, CA USA*

Congenital lipoid adrenal hyperplasia (lipoid CAH) is characterized by absent adrenal and gonadal steroidogenesis, 46,XY sex reversal, potentially lethal salt loss and grossly enlarged adrenals. Lipoid CAH was initially described as "20,22 desmolase deficiency", but in 1995 we showed it is caused by mutations in the steroidogenic acute regulatory protein (StAR). StAR is a short-lived, rapidly-produced protein that acts exclusively on the outer mitochondrial membrane to stimulate the import of cholesterol. The cholesterol is then converted to pregnenolone by the cholesterol side-chain cleavage enzyme, P450scc. Thus StAR acts as the acute trigger of steroidogenesis; by contrast, chronic regulation, which determines a cell's steroidogenic capacity, is determined by transcriptional factors determining the abundance of P450scc. Lipoid CAH patients of both karyotypic sexes have a female phenotype, but pubertal-aged 46,XX patients experience breast development and anovulatory menses, which is explained by a two-hit model. The first hit is loss of StAR and the acute steroidogenic response, but some StAR-independent steroidogenesis persists; the second hit is death of the steroidogenics cell secondary to accumulation of cholesterol and its auto-oxidation products. The normal ovary is steroidogenically quiescent from fetal life to the pre-adolescent, hence the ovary affected with lipoid CAH does not experience the second hit until the time of pubety. At puberty, gonadotropins recruit individual undamaged follicles monthly, producing small amounts of estrogen by StAR-independent steroidogenesis, leading

to breast development and anovulatory cycles. We have also found that milder StAR mutations that retain partial function cause non-classical lipoid CAH, in which salt loss is not clinically apparent, 46,XY patients have a male phenotype, and signs of hypergonadotropic hypogonadism are subtle. We have also discovered rare defects in P450scc that are hormonally and clinically indistinguishable from lipoid CAH, but which lack the massive adrenal hyperplasia that characterizes most, but not all, cases of lipoid CAH.

2. "Side Chain Cleavage Enzyme Defects - Varied and Unexpected Phenotypes"

Eli Hershkovitz, ***Ben Gurion University of the Negev***

The cholesterol side-chain cleavage enzyme P450scc, encoded by *CYP11A1*, converts cholesterol to pregnenolone to initiate steroidogenesis. P450scc deficiency can disrupt adrenal and gonadal steroidogenesis, only 19 such patients have been reported. Surprisingly, their clinical phenotype showed variable presentation including reaching unexpected term gestations in most pregnancies and developing normal male genitalia in some genetic XY males. When considering the patient with combined mineralocorticoid and glucocorticoid deficiency, an initial task is to determine whether or not the patient also has gonadal failure, which then suggests an early defect in steroidogenesis rather than an adrenal hypoplasia syndrome. The clinical presentation and hormonal findings in classic and nonclassic P450scc-deficient patients are indistinguishable from those with classic and nonclassic lipoid CAH, but patients with lipoid CAH typically have massively enlarged adrenals, whereas those described with P450scc deficiency have had small adrenals. However, the only definitive way to distinguish deficiencies of P450scc and StAR reliably is by DNA sequencing.

3. "Biological Relevance of TSPO - Steroid Interactions"

Moshe Gavish, ***Technion - Israel Institute of Technology***

The mitochondrial 18 kDa Translocator Protein (TSPO) was first detected by its capability to bind benzodiazepines in peripheral tissues and later also in glial cells in the brain, hence its previous most common name peripheral benzodiazepine receptor (PBR). TSPO has been implicated in various functions, including apoptosis and steroidogenesis, among others. Various endogenous TSPO ligands have been proposed, for example: Diazepam Binding Inhibitor (DBI), triakontatetraneuropeptide (TTN), phospholipase A2 (PLA2), and protoporphyrin IX. However, the functional implications of interactions between the TSPO and its putative endogenous ligands still have to be firmly established. The TSPO has been suggested to interact with a mitochondrial protein complex, summarized as mitochondrial membrane permeability transition pore (MPTP), which is considered to regulate the mitochondrial membrane potential ($\Delta\Psi m$). In addition, the TSPO is associated with several other proteins. The associations of the TSPO with these various proteins at the mitochondrial membranes have been attributed to functions such as apoptosis, steroidogenesis, phosphorylation, reactive oxygen species (ROS) generation, ATP production, and collapse of the $\Delta\Psi m$. Interestingly, while TSPO is known to play a role in the modulation of steroid production, in turn, steroids are also known to affect TSPO expression. As with the putative endogenous TSPO ligands, the effects of steroids on TSPO functions still have to be established. In any case, steroid-TSPO interactions occur in organs and tissues as diverse as the reproductive system, kidney, and brain. In general, the steroid-TSPO interactions are thought to be part of stress responses, but may also be essential for reproductive events, embryonic development, and responses to injury, including brain injury. The present review

focuses on the role of TSPO in cell death i.e. the notion that enhanced expression and/or activation of the TSPO leads to cell death, and the potential of steroids to regulate TSPO expression and activation.

4. "StAR Impact on Mitochondria: Remodeling the Organelle Protein Quality Control Machinery"

Joseph Orly, Assaf Bahat, Naomi Melamed-Book, Shira Perlberg, ***the Hebrew University of Jerusalem***

Steroidogenic cells express a mitochondrial matrix protein known as steroidogenic acute regulatory protein (StAR) that is essential for high output production of vital steroid hormones in the adrenal cortex and the gonads. StAR activity facilitates mobilization of cholesterol from the outer to the inner mitochondrial membranes where the sterol serves as substrate for steroid biosynthesis. It is currently accepted that import of StAR to the mitochondrial matrix rather terminates the cholesterol mobilization activity of the protein. Consequently, steroidogenic mitochondria rapidly accumulate exceedingly high matrix content of StAR protein calling for a rapid clearance. Previous and the present studies show that LON protease is the first of several predicted mitochondrial proteases that degrade StAR, including the m-AAA membrane metalloproteinase complex of AFG3L2/SPG7. We show that StAR accumulation in the mitochondria generates a yet to be found mitochondria-to-nucleus signaling leading to activation of the protease genes engaged in StAR degradation. Such adaptive changes of the mitochondrial protease content is not only physiologically relevant in steroidogenic ovary cells in vivo, but also constitute a functional response of the organelles in any cell type made to overexpress StAR. StAR induced transcriptional response does not include protease genes that are not involved in StAR degradation, such as CLP protease that resides in the matrix similar to LON. Consistent with such specificity hallmark is the fact that in order to upregulate LON, AFG3L2 and SPG7, StAR must be present in the matrix compartment; StAR mutants that do not enter the matrix, such as C28-StAR or N47-StAR are ineffective. Also, the transcriptional response to StAR is not dependent on the cholesterol mobilization activity of StAR since a naturally occurring loss-of-function StAR mutant, A218V, induces the protease gene activation equally well as the wild-type protein. Taken together, this study unraveled a novel regulatory loop, whereby acute accumulation of an apparently nuisance protein in the matrix provokes mitochondria-to-nucleus signaling that, in turn, activates specific transcription of genes encoding the mitochondrial proteases relevant for the enhanced clearance of the protein client.

Symposium: "Transition in Endocrine Care"

1. "Transition of Care for Chronic Endocrine System Disorders: the Examples of Type 1 Diabetes Mellitus and Growth Hormone Deficiency"

Alan D. Rogol, *University of Virginia, VA USA*

Transition is a process, whereas transfer is a single event. The goals of the transition process are: 1) That it is seamless; 2) Patient and family centered; 3) Outcome driven. It should be planned, gradual and chronologically and developmentally appropriate. The critical steps are to begin to write a transition plan by early adolescence, to have a medical summary that is both current and accessible and to find an endocrinologist to assume responsibility for the care of the emerging adult. The existing literature is generally devoid of rigorous evidence and thus our approach is to provide a "toolbox" rather than formal guidelines. There are barriers at each step of the process related to: patient, parent/family, adult provider and the health system, itself. The goals of today's presentation are to present background data to frame the problem of health care transitioning of young adults using mainly type 1 diabetes mellitus, but also growth hormone deficiency, including thoughts about dosing of GH as examples to summarize The Endocrine Society Transition Task Force's approach to transition resource development and to introduce new transition "tools" and resources for patients. These include: Health Care Transition: Recommended approach to planning for the pediatric practice; Provider assessment of patient skill set; A recommended approach to the adolescent transitioning to your adult practice; "Welcome to the practice" patient guide; Visitor information form; "Do you have questions". These tools are available to all at: http://www.endosociety.org/clinicalpractice/transition_of_care.cfm

2. "Transition Clinic at Sheba Medical Center: Principles and Results"

Ohad Cohen and Yael Levy-Shraga, *Sheba Medical Center*

3. Roundtable discussion: "Is a child a small adult?"

Amnon Zung, *Kaplan Medical Center*

Participants: Alan Rogol, Naomi Weitntrob, Ohad Cohen, Yael Levy-Shraga, Joel Singer

Symposium: "Pregnancy and Endocrinology"

1. "Basal Insulins in Pregnancy - Old vs. New Players"
Moshe Zloczower, ***Rambam Medical Center***

2. "Management of Pituitary Tumors in Pregnancy"
Yoel Toledano, ***Rabin Medical Center***

3. Bariatric Surgery: Impact on Pregnancy"
Yariv Yogev, ***Sackler Faculty of Medicine, Tel Aviv University***

Symposium: "Osteoporosis"

1. "Treatment of the Early Post-menopausal Woman: Update on HRT and SERM Therapies"

Yaron Rabinovitch, *Sheba Medical Center*

2. "The Use of Bone Turnover Markers in the Treatment of Osteoporosis"

Sophia Ish-Shalom, *Rambam Medical Center*

Bone tissue is not readily accessible for evaluation. Bone metabolism is characterized by two opposite activities couples in a basic multicellular unit (BMU), osteoclasic bone resoption and osteoblasic bone formation that constitute the process of bone turnover (BT). Changes in the in BT during growth and development are characteristic of normal bone physiology. Usually there is a marked increase in BT after menopause and in various disease states. Use of antiresorbing agents leads to a rapid decrease in the number of functioning BMUs and in BT. Increase in BT occurs during anabolic treatment. Several markers of BT(BTM) have been developed over the past 20 years that reflect the overall rate of bone formation and/or bone resorption. Most are immunoassays using antibodies that recognize specifically a component of bone matrix (i.e. type I collagen or non-collagenous proteins) that is released in the bloodstream during the process of either osteoblastic bone formation or osteoclastic resorption. Other assays recognize an enzymatic activity associated with the osteoblast. (bone alkaline phosphatase) or the osteoclast (tartrate resistant acid phosphatase). The analytical variability depends on BTM and the measurement method. The preanalytical variability has strong effect on BTM level. Several studies suggest that, in general, the larger the decrease in turnover markers with anti-resorptive agents, the greater the reduction in fracture risk. Thus, failure to observe a change in these response variables might be considered as a failure to respond to treatment or poor adherence. Achievement of BTMs level within low premenopausal range in a patient with moderate fracture risk after prolonged bisphosphonate treatment may facilitate the decision about "drug holiday".

The role of bone markers in monitoring response to treatment has been recently reviewed by the International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine that issued a recommendation for serum C- telopeptide of type I collagen (βCTX) and serum procollagen I N-propeptide (PINP) to be used as reference markers, due to their relative analytic and preanalytic stability. In spite of the increasing use of BTM's in clinical practice, more research is required using standardized analytes before robust evidence-based recommendations can be given.

3. "Bisphosphonates for Osteoporosis: Issues of Timing, Time limits and Alternatives"

Iris Vered, ***Sheba Medical Center***

Aminobisphosphonates have been used to prevent osteoporotic fractures for nearly two decades. Their long skeletal residence made possible unique intermittent dosing regimens, while raising concerns regarding possible detrimental effects due to accumulation in bone.

The fracture reduction efficacy of bisphosphonates was a primary outcome in pivotal, phase III registration trials, with a duration of up to 3 years. Fracture data were collected for up to 10 years in extension trials, as exploratory or safety outcomes. Fracture efficacy did not deteriorate over time, however, it seems that most of the of the effect on fractures is achieved within initial 3- 5 year treatment period and retained for additional several years after discontinuation (3-5 years, depending on the specific bisphosphonate). In a retrospective cohort study based on the administrative claims of a large U.S. health care organization the rate of hip fracture was increased significantly after discontinuation of bisphosphonates among women who were compliant with therapy for 2 years. This association was attenuated with higher compliance and a longer duration of previous therapy.

A cumulative use of bisphosphonate treatment has been implicated in uncommon adverse outcomes, such as osteonecrosis of the jaw, esophageal cancer and "atypical" femur fractures. The evidence with regard to long-term exposure is conflicting.

In the absence of robust data from clinical trials, empiric approaches are necessary to guide long-term treatment, including potential ‘‘drug holidays". The use of bone mineral density and biochemical markers of bone turnover may provide information about the persistence of the effect of the retained bisphosphonate after discontinuation. Estimation of fracture risk after discontinuation, using algorithms initially developed for untreated individuals may be useful to assess the need for retreatment.

A variety of drugs have been tested in patients previously treated with bisphosphonates. None of these studies addressed patients who had unsatisfactory treatment results. Fracture outcomes in those trials were an exploratory end-point and were either negative, positive or nonexistent.

In summary: While the limited-term benefits of bisphosphonate treatments for osteoporosis clearly outweigh the risks, there is limited evidence regarding the safety and efficacy of long-term treatment, or its discontinuation. Acknowledging the limitations of the current data, algorithms for long-term management of individuals based on risk stratification can be proposed.

4. "The Effects of Diabetes and its Treatments on the Skeleton"

Rivka Pollak-Dresner, ***Hadassah-Hebrew University Medical Center, Jerusalem***

Diabetes mellitus adversely affects the skeleton and is associated with an increased risk of osteoporosis and fragility fractures. Patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are at increased risk, although T1DM affects the skeleton more severely. Meta-analyses that evaluated studies involving 1.3 million participants reported odds ratios of 6.3-6.9 and 1.4-1.7 for hip fractures in patients with T1DM and T2DM, respectively. Risk factors for fractures include nephropathy in T1DM, and neuropathy, nephropathy, insulin treatment and disease duration>10yrs in T2DM.

The pathogenesis of skeletal fragility in T1DM and T2DM is different. Patients with T1DM have reduced bone mass as a result of inadequate accrual of peak bone mass, decreased bone formation and osteoblast function during skeletal growth. The “insulinopenia” hypothesis suggests that insulin exerts a bone anabolic effect, leading to low bone mass in T1DM. Other β cell products such as amylin and preptin are osteotropic and are also lacking in TIDM. On the other hand, bone mineral density is increased in patients with T2DM, but bone quality is decreased. Chronic hyperglycemia and increased concentrations of advanced glycation end products are associated with increased fracture risk. Although DXA is the standard method for the assessment of bone mass and strength, novel technologies such as trabecular bone score (TBS) better assess bone quality and fracture risk in patients with diabetes. FRAX underscores fracture risk in T2DM patients.

Recommendations for management of osteoporosis in patients with diabetes mellitus are based on extrapolation from recommendations for osteoporotic patients without diabetes rather than evidence-based guidelines. These include control of hyperglycemia and prevention of diabetic complications especially nephropathy. Intensive insulin therapy for T1DM if not contraindicated is associated with improved skeletal health. Calcium 1200mg/day preferably from diet is recommended. Hypercalciuria accompanying glucosuria may require higher Ca doses. Optimal serum 25-hydroxyvitamin D level in diabetic patients is unknown, but a target of 75nmol/l is recommended. Obese T2DM patients may require higher vitamin D doses. Whether vitamin D supplementation improves metabolic and vascular parameters needs to be prospectively assessed. Metformin and DPP-4 inhibitors have favorable skeletal effects, while glitazones should be avoided in T2DM postmenopausal women. Prospective randomized studies on the efficacy of bisphosphonates, 1-34 PTH, denusumab and stronstium ranelate in diabetic patients with osteoporosis are lacking, however retrospective studies suggest that established osteoporosis drugs are effective in diabetic patients. Oral hygiene should be optimized to reduce the risk of ONJ with bisphosphonates and denusumab.

Symposium: "Stem Cells in Endocrine Research"

1. "Ex-vivo generation of insulin-producing cells for beta-cell replacement in diabetes"

Shimon Efrat, *Department of Human Molecular Genetics and Biochemistry, Tel Aviv University*

Beta-cell replacement represents an attractive prospect for diabetes therapy. Given the shortage of human pancreas donors, research has aimed at generating alternative sources for human beta-like insulin-producing cells, by ex-vivo expansion of human islet beta cells, differentiation of pluripotent stem cells, and nuclear reprogramming of non-beta cells. Ex-vivo expansion of adult human beta cells results in loss of cell phenotype. Lineage tracing has shown that human beta cells survive, dedifferentiate, and significantly replicate in vitro. Dedifferentiation resembles epithelia-mesenchymal transition (EMT). Epigenetic analyses suggest that the dedifferentiated cells preserve the beta-cell epigenome. Recent findings demonstrate that these cells can undergo significant redifferentiation in vitro into insulin-producing cells. Our current efforts focus on improvement of redifferentiation efficiency by manipulating signaling pathways involved in EMT. This work may enable the generation of an abundant source of human insulin-producing cells for transplantation into patients with type 1 diabetes, given adequate immune protection means, as well as into type 2 diabetic patients. In addition, these human insulin-producing cells can be used in basic research, toxicology studies, and drug screening.

2. "Autologous Cell Replacement Therapy for Diabetes by Adult Cell Reprogramming"

Sarah Ferber, *Sheba Medical Center*

3. "Hormonal Regulation of Germ Line Stem Cell Establishment"

Lilach Gilboa, and Dana Gancz, *Weizmann Institute of Science*

Stem cell activity is essential for organ homeostasis and for regeneration following injury or disease. Many of the signals received by stem cells originate from their close supportive environment (niche), which controls their proliferation, maintenance and differentiation. However, accumulating evidence suggest that the endocrine system also participates in all aspects of stem cell biology.

In the fruit fly Drosophila melanogaster, germ line stem cells (GSCs) cooperate with their somatic niche cells to support continuous oogenesis. We found that two hormones: Insulin and the steroid hormone ecdysone are required for the establishment of both niche cells and GSCs. Somatic niches and their attached GSCs are established during larval development from somatic precursors and primordial germ cells (PGCs), respectively. During early larval stages, ecdysone receptors act as repressors of the differentiation of both precursor cell populations, allowing them a time window in which to proliferate. Proliferation rates of both somatic and germ cell lineages, and hence the final numbers of precursors, are determined by Insulin and Tor signaling. At late larval developmental times, ecdysone pulses induce the differentiation of the somatic niches. At an even later stage, a combination of somatic ecdysone and Insulin signaling non-autonomously induces PGC differentiation.

The work highlights several important points. First, systemic signals are intimately involved in organogenesis and the establishment of stem cell units. Second, while Insulin signaling has been mainly associated with cell proliferation, we show it has an important function in fate

determination as well. Third, formation of stem cell units (stem cells and their supportive niches) appears to require signals that act on all components of the unit. The great conservation of genes and biological principles between Drosophila and vertebrates suggest that mammalian stem cell units are similarly built, and that the hormonal status of the organism will have great influence on stem cell unit formation and perhaps on regeneration following medical manipulations.

Symposium: "Emerging Translation Aspects in Diabetes and Obesity Research"

1. "Novel targets of cytokine-induced beta cell death"

Yehiel Zick, *Department of Molecular Cell Biology, Weizmann Institute of Science*

2. Post-transcriptional Gene Regulation by MicroRNAs and RNA-binding Proteins in Obesity and Diabetes"

Hannah Kanety, ***Institute of Endocrinology, Sheba Medical Center***

3. "Diabetes and Cancer Risk: the Roles of Insulin and Cholesterol"

Derek LeRoith, *Rambam Medical Center*

Symposium: "New Developments in Thyroid Cancer"

1. "Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate FNA Cytology"
Richard T Kloos *(United States)*

2. "Robotic transaxillary thyroidectomy: indications, technique and patients outcomes"
Gideon Bahar, *Rabin Medical Center*

3. "Radioactive iodine therapy: When, how and how much?"
Ohad Cohen, *Institute of Endocrinology, Sheba Medical Center*

4. "The role of modern biological treatments in advanced thyroid cancer"
Aron Popovtzer, *Davidoff Cancer Center*

Meet the Professor: "Emerging Role for microRNA in Endocrine Tissues"

1. "Regulation of beta-cell mass and identity by microRNAs"
Eran Hornstein, ***Weizmann Institute of Science***

2. "Regulating the regulators: transcriptional control of miRNA genes"
Michael Walker, ***Weizmann Institute of Science***

Meet the Professor: "Year in Pituitary"

1. "The year in Pituitary: summary and review of the latest advancements in the field",
Yona Greenman, ***Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center***

Meet the Professor: "Doping in Sport"

1. "Doping in sport with endocrine system active agents: An issue of Olympic proportions"
Alan D Rogol, ***University of Virginia, VA USA***

Meet the Professor: "Thyroid Cancer"

1. "Treatment of well differentiated thyroid cancer: open discussion on an index case"
Richard, T Kloos, ***Veracyte Inc. San Francisco, CA USA***

Oral Presentations

Oral Presentations I: Diabetes, Obesity and Metabolism

AMPK corrects ER morphology and function in stressed pancreatic beta-cells via regulation of the ER resident protein DRP1 (ID: 25)

Elected as best basic abstract

Jakob Wikstrom, *Tal Israeli, Etty Bachar-Wikstrom, Yafa Ariav, Erol Cerasi, Gil Leibowitz. Hadassah Hebrew University Hospital*

Introduction: Lipotoxicity plays an important role in beta-cell failure in type 2 diabetes. Fatty-acid excess induces ER stress, which is accompanied by morphological changes. AMPK is an energy sensor, regulating metabolic stress; however its impact on ER morphology and function is unknown.

Aims: Studying the regulation of ER morphology by fatty acids and AMPK and their impact on beta-cell function and survival.

Methods: Mouse and human islets and INS-1E beta-cells were treated with and without palmitate and/or the AMPK activators AICAR and metformin. AMPK was inhibited using a dominant-negative AMPK adenovirus. ER and mitochondrial morphology were analyzed by super-resolution confocal and electron microscopy. The ER stress response and AMPK activity were analyzed by Western blot. Islet proinsulin and insulin content and secretion were analyzed by ELISA and RIA assays, respectively. Apoptosis was monitored by Western blot for cleaved caspase 3 and by nucleosome ELISA assay.

Results: Palmitate induced marked ER expansion and mitochondrial fragmentation. We demonstrate that DRP1, a key regulator of mitochondrial fragmentation, is an ER resident and plays an important role in this process. Inhibition of DRP1 in beta-cells attenuated fatty acid-induced ER expansion and mitochondrial fragmentation. Stimulating AMPK inhibited DRP1 by phosphorylating its Ser637 and completely prevented the alterations in ER and mitochondrial morphology. Strikingly, photo-bleaching of GFP-labeled DRP1 showed that DRP1 in the ER of stressed beta-cells translocated to mitochondrial fission sites. Further, palmitate-induced ER enlargement was associated with proinsulin retention in the ER, resulting in impaired proinsulin trafficking and processing. Stimulation of AMPK prevented these alterations.

Conclusions: AMPK-DRP1 is a novel pathway regulating ER and mitochondrial morphology, thereby controlling the response of beta-cells to metabolic stress. DRP1 may function as a node integrating signals from stress regulators, such as AMPK, to coordinate organelle shape and function, and as such could be viewed as an attractive therapeutic target in diabetes.

Paradox in metabolic homeostasis: AHNAK knockout mice are resistant to diet-induced obesity and yet they display reduced insulin sensitivity (ID: 47).

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Introduction: Insulin resistance is an underlying factor in the relation between obesity and diabetes. Using in vitro analyses, we have recently identified AHNAK protein as a negative regulator of GLUT4 expression and function. Accordingly, we have observed elevated AHNAK levels in adipocytes obtained from animal models of obesity/diabetes and obese/diabetic human subjects.

Aims: To understand the role of AHNAK in overall metabolic homeostasis, we have used AHNAK knockout (KO) mice.

Methods and Results: Compared to the regular chow wild type (WT), KO mice displayed 15% reduced body weight (BW), 65% lower fat mass and 12% increased lean body mass. Upon challenge with high fat-diet (HFD) for 12 weeks, KO mice were protected from HFD-induced obesity compared to the WT (50% reduced fat mass, 25% reduced BW and 37% increased lean body mass vs. WT). Even though fasting glucose levels were similar in WT and KO chow groups, KO-chow were glucose intolerant compared to WT-chow as evidenced by sustained elevated glucose levels in IPGTT. Compared to WT-HFD mice, KO mice exhibited higher fasting blood glucose levels (WT- 158 vs. KO - 180 mg/dL), and similar extent of impaired glucose intolerance (120' post glucose load- WT- 184 vs. KO- 211mg/dL). Interestingly, plasma insulin levels were approximately 50% lower in the KO mice on either diet compared to WT. Insulin tolerance test revealed reduced insulin sensitivity in the KO on HFD compared to WT mice. Contrary to the in vitro results, Glut4 levels in WAT obtained from KO mice on either chow or HFD were reduced (35% or 20% vs. 100% WT-chow). Gene expression studies showed that KO mice have increased levels of a) lipogenic enzyme SCD1 in liver, muscle and WAT, b) gluconeogenic enzyme G6Pase, c) insulin resistance-promoting adipokine RBP4 in WAT. However, expression of adipokines MCP1, TNFα and leptin that were about 4-fold increased in WT-HFD mice were similar to or lower in KO-HFD compared to WT-chow.

Conclusions: Thus, AHNAK-KO mice show dissociation between diet-induced obesity and insulin sensitivity. Taken together, our data suggests that while AHNAK has an important role in weight regulation, its deficiency impairs insulin sensitivity in vivo.

Neonatal Wolfram syndrome: novel de-novo dominant mutation presenting as an unusual clinical phenotype (ID: 52)

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Background: Wolfram, known also as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness) syndrome (WS) is a rare neurodegenerative disorder resulting usually from biallelic WFS1 gene mutations. Diabetes mellitus usually its first symptom, rarely presents prior to 1y of age.

Clinical and molecular studies: Exome sequencing was performed on a 5.9 years old boy from a consanguineous Palestinian family. He presented neonatally at 40d of age with persistent neonatal diabetes, bilateral cataracts, congenital (prelingual) deafness and left hydronephrosis. During follow up he developed failure to thrive, microcephaly, severe psychomotor retardation, seizures, severe scoliosis and bilateral lower limbs contractures. Laboratory investigations revealed normal serum electrolytes, lipase and thyroid function tests, normal urine osmolality, low serum insulin levels, negative anti insulin antibodies, normal pancreas by sonogram, 46,XY karyotype, and normal sequencing of the KiR6.2 gene. Whole exome sequencing revealed a heterozygous, c.923 C>T (p. S308F) novel, de-novo, missense mutation in an evolutionary conserved amino acid of WFS1, that was defined damaging by predicting softwares. Although wolframin 1's function has not been established its known formation as an oligomer suggests, that a dominant negative effect may cause the severe phenotype.

Conclusion: A novel de-novo heterozygous WFS1 mutation causes a unique and severe WS with cataracts, deafness and diabetes mellitus presenting neonatally. The clinical application of next-generation sequencing technology enhanced the diagnosis of a rare genetic disorder in a patient with atypical presentation and may have a role in defining new clinical manifestations of rare syndromes, such as WS.

Importance of maintaining redox potential balance in the development of type 2 diabetes (ID: 61)

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Background: Meta analyses conclude that antioxidant supplementations have no beneficial effects on the prevalence of type 2 diabetes (T2D). These disappointing results conflict with most in-vitro and in-vivo studies showing damage of oxidative stress and benefits of antioxidants on insulin sensitivity and β-cell function. We assume that there is an optimal redox state that normally should be maintained. If shifted, disturbances in β cell function and insulin sensitivity appear. The aim of this study is to clarify the dose-response effect of antioxidant supplementation on the progression of T2D.

Materials and methods: Both in-vitro and in-vivo experiments were conducted. In-vitro study was performed on insulinoma cell lines. Dose response effects of H_2O_2 and the antioxidant N-acetyl-L-cysteine (NAC) were investigated on insulin secretion, β-cells viability and mRNA expression of specific transcription factors. In-vivo experiments were conducted on KK-A^y mice, a model of T2D. Mice were given NAC at different concentrations (200-1800 mg/kg/day). Plasma TBARS were measured as an indication for oxidative stress. Diabetes was evaluated in treated mice by glucose and insulin tolerance tests, histological studies of pancreatic β-cells, plasma insulin was measured and insulin signaling pathway was followed in muscle tissue.

Results: In-vitro experiments show that, whereas high concentrations of H_2O_2 induce oxidative stress and pancreatic b-cell death, low concentrations (4μM) increased viability of these cells, and basal and glucose-induced insulin secretion. High concentrations of NAC reduced viability of cells. mRNA expression of Pdx1 and Pax4 is regulated by the redox state of cells. In-vivo results show that while 600, 1200 and 1800 mg/kg/day NAC were all found to improve glucose tolerance of mice, the 1200 mg/kg/day treatment was the most effective in improving insulin sensitivity as indicated by low HOMA-IR.

Conclusions: Alterations in redox balance, resulting from oxidative stress as well as oversupply of antioxidants, may lead to disturbances in pancreatic β-cells function and in insulin sensitivity. The inconsistency in literature regarding antioxidant and prevention of diabetes may result from the lack of clear guidelines for effective doses. There is a need to find certain biomarkers for the target oxidative state that should be maintained in order to obtain optimal outcomes.

Omentin, a novel adipokine with insulin-sensitizing properties is associated with insulin resistance indices in normal gestation (ID: 87)

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Objective: Omentin, a newly identified adipokine, is predominantly expressed and secreted by visceral adipose tissue. Omentin enhances insulin mediated glucose uptake in human adipocytes thus inducing systemic insulin-sensitizing effect. The aims of this study were to determine whether circulating maternal omentin concentrations are associated with insulin resistance indices and to assess which compartment, maternal, fetal or placental, is the source of omentin in maternal circulation.

Methods: Fasting serum glucose, insulin and omentin were determined in 25 healthy pregnant women at the third trimester, before and 3 days after elective cesarean section. Cord blood omentin were also measured in their 25 neonates. The Homeostasis Model Assessment (HOMA) was used to evaluate insulin sensitivity before and after delivery. Non parametric statistical methods were employed.

Results: Antepartum maternal omentin concentrations were negatively correlated with insulin (r= -0.41, p=0.04) and insulin resistance (HOMA-IR, r= -0.41, p=0.038) and positively correlated with insulin sensitivity (HOMA-%S, r=0.4, p=0.04). Post-partum omentin were negatively correlated with maternal BMI (r= -0.44, p=0.02), antepartum HOMA-IR (r= -0.49, p=0.01), and beta cell function (HOMA-%B, r=0.47, p=0.01). Median maternal omentin concentrations was comparable before and after delivery (57.2, IQR: 38.2-76.2 vs. 53.4, 39.8-69.4, respectively, p=0.25) and highly correlated (r=0.83, p<0.001). Maternal and neonatal omentin concentration did not differ significantly (fetal: 62.2, 44.3-74.2, p=0.77) and were not correlated (r=0.1, p=0.6).

Conclusions: Circulating maternal omentin concentrations are correlated with insulin resistance indices suggesting that this adipokine may be implicated in pregnancy-related insulin resistance. The comparable anteparum and postpartum maternal omentin concentration, and the strong correlation between pre- and post delivery levels, as well as the lack of association between maternal and neonatal omentin concentrations, suggest that the placenta or fetal compartment are unlikely the source of circulating maternal omentin. Collectively, these finding suggest that omentin may play a role in metabolic adaptations of normal gestation and that its source is maternal tissues.

Acute hyperglycemia in type 1 diabetes mellitus is associated with simultaneous changes in electrical brain activity (ID: 100)

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Objective: to study the association between episodes of diurnal and nocturnal asymptomatic acute hyperglycemia and brain function abnormalities, assessed by electroencephalographic (EEG) changes, in young patients with Type 1 diabetes mellitus (T1DM).

Research Design and Methods: Ten youths, mean age 14.2±1.9 years, with T1DM for 5.57±3.54 years, were monitored simultaneously and continuously for 40-48 hours by EEG and interstitial glucose concentration (IGC) monitoring, while retaining their regular activities, food intake and insulin regimen. The artifact-free EEG was quantitatively analyzed and the EEG powers of waves' frequencies were compared between various glycemic ranges per individuals and for the pooled data.

Results: Amongst the total 1253 combined simultaneous measurements of IGC and EEG, 27% were in the moderate hyperglycemia range (200-280 mg/dl) and 18.6% in the severe hyperglycemia (>280 mg/dl). Mean IGC was 206.95±94.8 mg/dl. The correlation between EEG power of different waves' frequencies and IGC varied between subjects. Severe hyperglycemia during wakefulness was associated with increased EEG power of low frequencies and with decreased EEG power of high frequencies. Hyperglycemia during sleep was associated with increased EEG power of low frequencies in all brain areas and of high frequencies in frontal and central areas.

Conclusion: This is the first study to demonstrate that electrical brain activity differs significantly during asymptomatic acute hyperglycemia when compared to normoglycemia.. Clinical emphasis on hyperglycemic excursions is suggested. Future study is required to understand the effect of those changes on cognitive function and sleep pattern

TM7SF3 - a Novel Receptor that Affects Beta-Cell Survival and Resistance to ER Stress (ID: 101)

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Introduction: Pro-inflammatory cytokines induce death of pancreatic beta cells, leading to the development of type 1 diabetes.

Methods and results: A high-throughput screen of 3,850 mouse small interfering RNAs (siRNAs) in cytokine-treated MIN6 beta cells conducted in our lab revealed a novel gene, TM7SF3, which regulates beta cell death. Tm7sf3, (Transmembrane 7 superfamily 3) encodes an orphan seven transmembrane receptor with an unknown function. Silencing of TM7SF3 promotes death of MIN6 cells and human pancreatic islets, abrogates the glucose-stimulated insulin secretion (GSIS) in these cells, promotes proteosomal-degradation of IRS-2 protein, impairs insulin signaling in beta cells, increases iNOS mRNA as well as iNOS activity (by nitric oxide production, ~2-fold) and results in a marked ~3-fold increase in the transcription of CHOP, a key element in the execution of the unfolded protein response (UPR) of the ER. On the other hand, overexpression of TM7SF3 reduces caspase activity in human islets and improves GSIS by 50%.

Conclusions: These findings implicate TM7SF3 as a potential new player in the inhibition of beta-cell death. In addition, TM7SF3 plays a role in protection of IRS-2 from degradation and in promotion of insulin secretion in pancreatic beta cells.

Induction of cytosolic phospholipase A2α is required for adipose neutrophil infiltration and hepatic insulin resistance early in the course of high fat feeding (ID: 108)

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Background: While in established obesity adipose tissue inflammation likely contributes to dysfunctional fat-liver crosstalk, whether this occurs in short-term adaptation to dietary surplus is unclear.

Aims: Here we set to explore if the adipose tissue infiltration by neutrophils that occurs 3-7d after initiating high-fat diet (HFD) could contribute to the early occurrence of hepatic insulin resistance and to determine the role of cytosolic phospholipase$A_2\alpha$ ($cPLA_2\alpha$) in this process.

Results: HFD for 3 days (3dHFD) caused a significant upregulation of $cPLA_2\alpha$ in peri-epididymal fat and the liver. A specific antisense oligonucleotide (AS) effectively prevented $cPLA_2\alpha$ induction and neutrophil infiltration into adipose tissue, an effect likely involving MIP-2. AS also protected against 3dHFD-induced hepatic insulin resistance. To sort out the role of adipose neutrophil infiltration in hepatic insulin resistance (independent of $cPLA_2\alpha$ induction in the liver), mice were intraperitoneally injected with anti-ICAM-1 antibodies. This effectively prevented neutrophil infiltration without affecting $cPLA_2\alpha$ or MIP-2 expression. Nevertheless, similarly to AS, 3dHFD-induced hepatic insulin resistance was prevented. Adipose tissue secretion of TNFα was increased by 3dHFD and was prevented by AS or ICAM-1 antibodies treatment.

Conclusion: We propose that an acute, $cPLA_2\alpha$ dependent neutrophil-dominated inflammatory response of adipose tissue contributes to hepatic insulin resistance in short-term hyper-nutrition.

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Oral Presentations II: Thyroid and Adrenal

Angiotensin 1-7 modulates the aldosterone response to salt restriction in rats: A renin-independent mechanism? (ID: 79)

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Background: Angiotensin 1-7 (Ang1-7) antagonizes many of the cardiovascular effects of Angiotensin II (AngII), including major effects as the induction of vasodilation. We have recently reported that Ang1-7 attenuates the increase in circulating renin and aldosterone (aldo) induced in high-fructose-low magnesium diet, a model of metabolic-syndrome. Whether or not the reduction in aldosterone was a sequel of the decrease in renin remained unclear, particularly since we also show that the receptor for Ang1-7, Mas, is clearly expressed in the adrenal zona glomerulosa.

Aim: To study the effect of Ang1-7 administration in- vivo on the renin and aldo response to salt restriction in rats.

Methods: Rats were kept on either normal chow or low salt diet (Teklad Rat Diet 7034 Harlan, low sodium water, Neviot) for one week, during which either vehicle or Ang1-7 was continuously infused through Alzet pumps (576 µg/kg/day, s.c., n=6-7/group). Blood was drawn for plasma rennin and aldo concentration prior to the subdivision to dietary intervention as well as at the end of the experiment, following which animals were then killed to harvest the kidneys. Renal slices were prepared to assess ex-vivo renin release. Since rodents have low circulating angiotensinogen, all renin assays were carried out in media enriched with plasma from 24h nepherctomized rats.

Results: In rats fed on regular chow, Ang1-7 infusion had no effect on either plasma aldo or plasma rennin activity (RA). In rats fed on a low salt diet, aldo increased from 10±5 to 27±8ng/dl ($p<0.002$), but this increase was attenuated by Ang1-7 infusion (16±4.7ng/dl, $p=0.02$). Plasma RA rose by 50-70% in salt restricted rats, which was not modified by Ang1-7 infusion. Renin secretion was higher in renal slices prepared from salt-deprived rats compared with rats fed on normal chow ($p=0.003$) and was increased in renal slices from Ang1-7 treated rats ($p<0.012$).

Conclusion: This is the first report showing that Ang1-7 is a negative modulator of the aldosterone response to salt deprivation and that this effect in unlikely to be mediated by the concordant curbing of the rise in rennin.

Androgen receptor CAG repeat length in relation to phenotype of females with non-classical 21-Hydroxylase deficiency (ID: 45)

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Context: Non-classical 21-hydroxylase deficiency (NC21OHD) is a mild form of congenital adrenal hyperplasia associated with different degrees of postnatal virilization developing from infancy to adulthood. NC21OHD arises from partial deficiencies of 21-hydroxylase activity. The variability of symptom severity, despite the similarity of CYP21A2 mutations, suggests the influence of other modifiers. The length of CAG repeats of the androgen receptor (AR) gene was found to be inversely correlated to transactivation activity of the human AR and to affect phenotypic features of several medical conditions characterized by hyper/hypo androgenism.

Objective: To investigate the associations between the CAG repeats and the severity of the phenotypic features of females with NC21OHD.

Design, subjects and methods: Determination of the CYP21 genotype, degree of virilization and length of CAG repeats in 119 females with NC21OHD. Since the two alleles of the AR gene located on the X chromosome are differentially expressed in females due to the X inactivation phenomenon, the X-weighted biallelic mean (X-WBM) was calculated based on CAG repeat length adjusted to percentage of X-inactivation.

Results: A longer (>25) X-WBM of the AR repeats positively correlated with older age at diagnosis (20.1 Vs. 15.2 yr, p=0.03), shorter height SDS at diagnosis (-0.12 Vs. 0.42 SDS, p=0.03), older age at adrenarche (9.7 Vs. 8.2 yr, p=0.02) and gonadarche (11.0 Vs. 10.0 yr, p=0.008), and lower severity score (10.9 Vs. 11.9, p=0.03).

Conclusion: The CAG repeat length of the AR gene correlates with several clinical characteristics of females with NC21OHD and can explain, at least in part, the diversity of their phenotype.

Thyroid normal levels: "normalization" causes abnormality (ID: 27)

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Background: Distribution of thyroid stimulating hormone (TSH) levels within populations is not normal. This is due to physiological changes that cause temporary increases in TSH during stress, illness and recovery thereof. Although this is physiological, methods to normalize the distribution are commonly used when defining normal limits.

Objective: To compare the normal limits defined by three normalization methods versus non-normalized distribution based on a large cohort with no known thyroidal illness.

Methods: Data were collected from a computerized data base of the Clalit health services in Jerusalem. Exclusion criteria were positive anti-thyroid peroxidase or anti-thyroglobulin antibodies and treatment with any drug. TSH values were normalized with the Hoffmann, Tukey and natural log transformation (NLT) methods. The lower normal limits (LNL) i.e. the 2.5th percentile and the upper normal limits (UNL), i.e. the 97.5th percentile were defined. The clinical relevance of the limits was tested by calculating the mean FT3 and mean FT4 for results of TSH below, within and above the limits for each method for each decade of life.

Results: We report the results of the 31-40 age group, based on 2578 subjects, as a representative example. According to the non-normalized, Hoffman, Tukey and NLT – the limits were 0.98-6.9, 0.97-4.32, 0.44-5.15 and 1.24-5.56 IU/l respectively, i.e. maximal reduction from non-normalized data occurred for the LNL by the Tukey method (55%) and for the UNL by the Hoffman method (37%). There was no difference in average FT3 or FT4 between patients with TSH within, below or above the normal range for all 4 methods.

Conclusions: Different normalization methods alter the normal limits by up to 55%. However, in individuals without thyroid illness, thyroid hormone values are stable over a wide range of TSH levels thus questioning the value of any normalization method.

Pregnancy outcomes in women with severe hypothyroidism (ID: 67)

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Background: Maternal hypothyroidism during pregnancy has been largely associated with a range of adverse obstetrical outcomes, mainly miscarriage and preterm delivery. Most studies to date have focused on mild or subclinical hypothyroidism during gestation.

Objective: To evaluate the incidence of severe hypothyroidism in pregnancy, related clinical factors, and impact on pregnancy outcome.

Methods: A retrospective case series performed at Maccabi Healthcare Services using the computerized database of 2009-2010. Files of all pregnant women were reviewed for serum TSH test results. The diagnosis of hypothyroidism was based on a serum TSH reference range of up to 2.5mIU/L in the first trimester and up to 3.0mIU/L in the second and third trimesters. Severe hypothyroidism was defined as serum TSH >20mIU/L detected during pregnancy. The electronic files of pregnant women with severe hypothyroidism and a control group of age-matched euthyroid pregnant women were reviewed for demographic and clinical data including all recorded obstetrical complications.

Results: Among 9872 pregnancies complicated with maternal hypothyroidism, maternal serum TSH>20mIU/L was detected in 103 pregnancies (1.04%). Most cases had an autoimmune etiology. All women were treated with levothyroxine (LT4) during pregnancy. Maximum serum TSH level ranged from 20.11mIU/L to 150mIU/L (median 32.95mIU/L), median level, from 0.36mIU/L to 75.17mIU/L (median 7.44mIU/L). Mean duration of hypothyroidism during pregnancy was 21.2±13.2 weeks (median 18.5 weeks), in 36 cases (34.9%), all recorded TSH levels during pregnancy were elevated. Rates of adverse pregnancy outcomes were as follows: abortion 7.7%, premature delivery 2.9%, other complications 14.5%. No significant difference was found in these outcomes between the study group and a control group of 150 euthyroid women. In the study group, median serum TSH level during pregnancy was negatively correlated with patient age ($p<0.05$), number of TSH tests during pregnancy ($p<0.01$), and LT4 dose at end of pregnancy ($p<0.05$). There was a positive association between rate of abortions+premature deliveries and rate of all pregnancy-related complications with median serum TSH level ($p<0.01$).

Conclusions: Abortions and premature deliveries occur infrequently in women with severe hypothyroidism. Intense follow-up and treatment may improve pregnancy outcome even in women who do not reach target TSH levels.

Predictors for thyroid carcinoma in Israel: A national cohort of 1,624,310 adolescents followed for up to 40 years (ID: 35)

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Introduction: Data on adolescent precursors of thyroid cancer in adulthood are scant.

Methods: In order to evaluate potential risk factors for thyroid cancer we linked two national data sources: the military recruitment health examinations and the Israel National Cancer Register. The study population (N=1,624,310 participants) included 1,145,865 Jewish males, aged 16-19 when examined between 1967 and 2005, and 478,445 Jewish females aged 16-19 when examined between 1989 and 2005. The cancer follow-up extended up to 2006. Multivariable Cox proportional hazards modeling was used.

Results: During 24,389,502 person years of follow-up 760 incidence cases of thyroid cancer were identified. The mean age at diagnosis was 25.2±4.2 years for women and 37.2±10.0 years for men. Women had a substantially higher incidence [birth cohort-adjusted hazard ratio (HR)=5.70 (95% CI 4.45- 7.31), $p<0.001$)]. Height predicted incidence in both sexes, with birth cohort-adjusted HRs of 1.03 ($p<0.001$) in males and 1.04 ($p<0.001$) in females, per 1 cm increment in height. In males, but not in females, there was a graded association between education, as measured by years of schooling, and incidence of thyroid cancer. BMI was not associated with incidence. In a multivariable analysis of 617,613 males and 469,185 females examined from 1989 onwards, which included sex, birth year, height, and education, the excess risk in females persisted strongly (HR= 5.54, 95% CI 4.30-7.13), as did the association with height.

Conclusions: Female gender, measured height in adolescence, and later birth cohorts were independent predictors of thyroid cancer in adults in Israel. Further study is needed to unravel the mechanisms whereby height is associated with thyroid cancer.

Vitamin D Receptor (VDR) expression is linked to the expression of the extracellular matrix protein 1 (ECM1) and the type II transmembrane serine protease TMPRSS4 in human thyroid papillary carcinoma (ID: 32)

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Background: Vitamin D receptor (VDR) is expressed in epithelial cells of the normal thyroid gland. Furthermore, the receptor exists in malignant dividing cells, which respond to 1,25 dihydroxy vitamin D by decreased proliferative activity in vitro. Genes that regulate cell-cell and cell-matrix adhesion and degradation of extracellular matrix have been screened as potential markers of malignant thyroid nodules. The mRNA expression level of two of them, the extracellular matrix protein 1 (ECM1) and the type II transmembrane serine protease TMPRSS4, was shown as an independent predictor of malignant thyroid neoplasms.

Aim: To assess the relationship between cell-matrix adhesion genes ECM1 and TMPRSS4, and VDR in patients with papillary thyroid carcinoma (PTC).

Methods: We quantified different mRNA gene expression in 21 PTC tissue samples (follicular variant of PTC [n=14], classical variant of PTC [n=7]) and in 21 normal thyroid tissue samples from the same patients harvested during thyroidectomy. Gene expression of EMC1, TMPRSS4 and VDR was measured using quantitative real-time-PCR. Gene expression was considered as up- or down-regulated in cancer tissue if it varied by more than 2-fold in malignant relative to the normal thyroid tissue from the same patient. Statistical analysis was performed using SPSS version 19.0. Correlation analysis of the genes expression was performed using the non-parametric Mann-Whitney U test and the non-parametric Spearman's rho.

Results: High ratio of expression of VDR between malignant/normal thyroid tissue in the same patient (3.06±2.9) was seen in thyroid specimens showing also high malignant to normal expression ration of ECM1 (17.27±33.85) or TMPRSS4 (192.17±204.09). There was an overall significant adjusted correlation between the expression ratio in malignant/normal thyroid of VDR and that of ECM1 ($R=0.648$, $P < 0.001$). In contrast, a normal malignant/normal thyroid tissue expression ratio of VDR (0.96±0.71) was observed in patients with low-normal expression ratios of TPMRSS4 and ECM1 genes.

Conclusions: In human thyroid cancer cells, increased VDR expression is often linked to increased ECM1 or/and TPMRSS4 expression, which calls for further studies with vitamin D analogs in persistent and recurrent thyroid carcinoma.

Small bone metastases seen on post-radioiodine ablation scans and have no structural correlate on imaging studies usually respond well to radioiodine and remain stable for years (ID: 55)

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Background: Bone metastases from differentiated thyroid cancer are generally resistant to commonly used activities of radioiodine (RAI) and are associated with poor prognosis. However, in a recent study from our group we noted a small subgroup of patients with RAI-avid bone metastases who had no structural correlate on imaging studies, and had no skeletal complications during follow-up. The goal of the current study was to describe the characteristics and the natural course of this subgroup of patients.

Patients and Methods: In a retrospective review of medical records at Memorial Sloan-Kettering Cancer Center 288 patients were identified with bone metastases from thyroid cancer between 1960 and 2011. Out of this group, 14 patients who had a RAI-avid bone metastasis with no structural correlate on CT or MRI were included in the study. Eighty six percent of patients had papillary thyroid carcinoma (11 patients), one had Follicular carcinoma, and 2 patients had Hurtle cell carcinoma.

Results: After a median follow-up period of 5 years (range 2-14 years) all patients were alive, none had evidence of structural bone metastases, and none had experienced skeletal related events. The final disease status was defined as NED in 5 patients (36%), stable biochemical persistence in 2 patients (14%), stable structural persistence (in the neck and/or lungs) in 6 patients (43%), and one patient with Hurtle cell carcinoma had slowly progressive pulmonary nodules over a follow-up period of 10 years.

Conclusion: RAI-avid bone metastases with no structural correlate on high resolution imaging studies often resolve following RAI treatment, do not cause skeletal related complications, and do not significantly affect prognosis. Recognition of this unusual type of bone metastases is important as it may prevent overtreatment, and allow a less aggressive approach to long term surveillance.

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Oral Presentations III: Bone, Vitamin D and Calcium Metabolism

Sirt1 regulates the generation of brown adipocytes (ID: 78)

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Background: Weight gain, visceral fat deposition and increased generation of white adipose tissue are the hallmark of aging. Increased marrow adipogenesis with aging also occurs and contributes to the development of osteoporosis. Adipose tissue is composed mainly of white adipocyte tissue (WAT) which is the storage site of excessive energy and the source of pro-inflammatory mediators. In addition, there is a small functionally discrete adipocyte subset brown adipose tissue (BAT) which dissipates energy as heat and combats obesity. Increased BAT is associated with beneficial health related-outcomes and a desired target.

The anti-aging gene SIRT1 stimulates PPARγ coactivator 1-alpha (PGC1α) expression, represses PPARγ, a master regulator of adipocyte differentiation, and modulates lipid homeostasis through deacetylation of the nuclear receptor liver X receptor (LXR). We reported that SIRT1 plays a role in determining the fate of the bone marrow mesenchymal progenitor cell to become an osteoblast or an adipocyte (Endocrinology 2011:152 4514-4524). Here we show that SIRT1 plays a role in the generation of brown adipocytes.

Results: Studies were conducted in whole vertebrae isolated from 5 months-old female $SIRT1^{+/-}$ mice and their WT counterparts, and in the murine embryonic mesenchymal stem cell line C3H10T1/2. mRNA was extracted from whole vertebrae including the bone marrow and mRNA expression of key markers of brown adipocytes was determined by real time RT-PCR. A dramatic decrease in the BAT characteristic genes was observed in $SIRT1^{+/-}$ mice: Uncoupling protein 1 (UCP1) (-75%), PGC1α (-50%), Deiodinase 2 (Dio2) (-70%), PRDM16 (-50%), Adiponectin (-60%).

Conclusions: Based on these findings we hypothesized that activation of SIRT1 by a synthetic sirtuin 1 activating compound (STAC) will stimulate "browning" of adipocytes. C3H10T1/2 cells were induced to adipogenesis with insulin, dexamethasone, indomethacin IBMX and rosiglitazone, in the presence of the STAC SRT2183 or a vehicle. mRNA expression of BAT markers was determined 24 hours post induction and oil red-o stainings were conducted 14 days post induction. The administration of SRT2183 significantly increased UCP1 expression (+50%), PGC1a (+200%) and Dio2 (+60%), and reduced the generation of white adipocytes. These results suggest that SIRT1 activation may stimulate the generation of brown adipose tissue in the marrow and elsewhere.

Older women with breast cancer are at higher risk for osteoporotic fractures and experience them at higher hip bone mineral density (BMD) levels than non-breast cancer patients. (ID: 68)

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Introduction: We and others have reported that women with higher BMD are at increased risk of developing breast cancer (BC).Additionally, the risk of breast cancer is lower among women with a prior hip or distal forearm fracture. However, data on the risk of osteoporotic fractures in women with breast cancer are conflicting. The objective of this study was to assess fracture risk adjusted for BMD in women with and without BC treated at Soroka University Medical Center (SMC).

Methods: The electronic medical charts of women who underwent DEXA BMD studies at SMC between February 2003 and March 2011 were screened for any diagnosis of an osteoporotic fracture (fracture of hip, humerus, ribs, spine or distal radius) diagnosed after BMD testing. Pathologic and high trauma fractures were excluded. Demographic, BMD and laboratory findings were compared in patients with and without fractures according to BC status.

Results: In 17165 patients with BMD tests (828 with BC), mean ages 70 [±9.3] and 71 [±10.8] respectively (P=0.623), 1443 osteoporotic fractures were recorded, including 72 in women with BC. Median time from BMD to first osteoporotic fracture was a 2.2 years (0.4-4.3 inter-quartile range, years). Median time from BC diagnosis to BMD was 6.4 years. BMD (g/cm^2) (0.86 ± 0.14 vs. 0.83 ± 0.14) and T score (-1.13 ± 1.15 vs. -1.43 ± 1.14) at the total hip were significantly higher in fracture patients with BC compared to those without BC (p value 0.026 for both). In subset analysis of fractures at specific sites, rib fractures occurred at a significantly lower total hip BMD and fractures of the humerus at a significantly higher spine BMD in women with BC. In a multivariable analysis adjusted for age, BMI and BMD, hazard ratio for any osteoporotic fracture in women with BC was 1.33 (p=0.026).

Conclusions: Breast cancer survivors are at increased risk of an osteoporotic fracture at higher BMD levels than counterparts without breast cancer. This increased risk of fracture might be explained by side effects of cancer therapy or possible effects of breast cancer on bone metabolism.

A long-term follow-up of patients with postoperative hypoparathyroidism (ID: 50)

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Background: Permanent hypoparathyroidism is an uncommon complication of thyroidectomy. There are currently no formal guidelines for its chronic management, and large cohort studies of its long-term course are lacking.

Objective: To characterize the course of post-thyroidectomy hypoparathyroidism in a large cohort of patients treated in a single medical center.

Methods: We conducted a retrospective chart review of consecutive patients diagnosed with permanent postsurgical hypoparathyroidism at a tertiary medical center. The patients had undergone thyroidectomy from January 1975 to October 2011 and were followed thereafter at the hospital's endocrine clinic. Data were collected on background factors, calcium/phosphorus homeostasis, and bone mineral density at the last visit, treatment patterns, and screening for renal and vascular complications by abdominal imaging.

Results: Complete data were available for 77 of the 97 patients who met the study criteria, 88% were female.. Mean age at the last visit was 60.5±13 years, and mean duration of follow-up was 12.9 years. Mean serum calcium level at the last visit was 8.5±0.6 mg/dl, and 11.8% of patents had urinary calcium levels of >300 mg/day. Ten percent had renal stones/nephrocalcinosis, and 15% had calcification of the abdominal aorta. Higher urinary calcium levels were significantly associated with higher dosages of calcium supplements and alpha-D3 ($p<0.01$). The rate of abdominal aortic calcification was associated with longer follow-up, higher calcium blood levels at the last visit, and higher spinal T scores ($p<0.05$). Higher T-scores of the spine and hip were associated with longer follow-up ($p<0.01$).

The effect of vitamin D on the inflammatory response of airway epithelial cells to cytokines prevalent in asthma (ID: 41)

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Background: There is a general agreement that airway inflammation is a critical component of asthma pathogenesis. Airway epithelial cells (AECs), as the first cells encountering allergens and pathogens, initiate inflammation by producing various cytokines and contribute to the propagation of inflammation by further secreting eosinophilic chemokines (e.g., CCL11) and neutrophilic chemokines (e.g., IL-8, GROα and ENA78) in response to the Th2-type cytokines IL-4 and IL-13 (characteristic of allergic asthma) and the Th1 cytokines TNF and IFNγ (characteristic of severe asthma and virally-induced asthma). Epidemiological studies report an inverse correlation between vitamin D status and the frequency and severity of asthma episodes. AECs were shown to contain 25(OH)D 1α-hydroxylase (CYP27B1) and can thus produce the active vitamin D metabolite, calcitriol, from the circulating vitamin D metabolite, 25(OH)D, at the site where intervention is mostly needed. Therefore we view the AEC as a most relevant cell to study the possible effects of vitamin D in the control of asthma.

Aims: 1. To examine the effect of calcitriol on the production of eosinophilic and neutrophilic chemokines by AECs treated with Th1 and Th2-type cytokines. 2. To assess the effect of inflammatory cytokines on the capacity of AECs to produce and respond to calcitriol.

Methods: The experimental model is the immortalized human AEC line BEAS-2B. The expression of chemokines, CYP27B1 and the vitamin D receptor (VDR) was determined by real time PCR.

Results: A 24 hour pretreatment of AECs with calcitriol inhibited the induction of CCL11 by IL-4, IL-13 and TNF, but did not affect the induction of IL-8, GROα and ENA78 by TNF and IFNγ. TNF and IFNγ separately and synergistically up-regulated CYP27B1. IFNγ alone and synergistically with TNF up-regulated VDR levels. The capacity of AECs to produce calcitriol was demonstrated by the inhibitory effect of the precursor, 25(OH)D on CCL11 induction.

Conclusions: The anti-inflammatory activity of vitamin D under an in vitro scenario of allergic asthma may explain the inverse correlation between vitamin D circulating levels and the frequency and severity of asthma episodes found in epidemiological studies and establishes the rational for inhalation treatment of asthma with calcitriol or 25(OH)D.

Decreased serum concentrations of 25-hydroxyvitamin D are associated with increased risk of progression to impaired fasting glucose and diabetes (ID: 63)

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Objective: To study the association between vitamin D status and the risk for incident impaired fasting glucose (IFG) and diabetes in a population-based cohort of diabetes-free subjects.

Research Design and Methods:A historical prospective cohort study following subjects over time from the "Clalit Health Services" (CHS) database, which includes information on nearly 4 million people. Diabetes-free subjects, age 40-70 with serum 25-hydroxyvitamin D (25-OHD) measurements were followed for 2 years to assess the development of IFG and diabetes by five 25-OHD subgroups (nmol/L: < 25,25.1-37.5, 37.6-50,and >75, ' and, 75 -50, and >75.)

Results: The baseline cohort included 117,960 adults: 83,526 normoglycemic subjects and 34,434 subjects with IFG. During follow-up 8,629 subjects (10.3% of the normoglycemic group) developed IFG and 2,162 subjects (1.8% of the total cohort), progressed to diabetes. A multivariable model adjusted for age, gender, population group, immigrant status, BMI, season of vitamin D measurement, LDL and HDL cholesterol, triglycerides, estimated GFR, history of hypertension and/or cardiovascular disease, Charlson co-morbidity Index, smoking and socioeconomic status revealed an inverse association between 25-OHD and the risk for progression to IFG and diabetes. The odds of transitioning from normoglycemia to IFG, normoglycemia to DM, and IFG to DM among subjects with 25-OHD level $\leq$ 25 nmol/L were greater compared to those with 25-OHD level >75 nmol/L: OR=1.13, CI:[1.03-1.24], OR=1.77, CI:[1.11-2.83] and OR=1.43, CI:[1.16-1.76], respectively.

Conclusions: Vitamin D deficiency appears to be an independent risk factor for the development of IFG and diabetes.

Atypical femoral fractures: radiological evaluation and bisphosphonate exposure (ID: 75)

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Evidence suggests that long term bisphosphonate (BP) treatment predisposes to atypical fractures (AF), but the question of causality remains open. The attempt to answer this question begins with case identification. The current case definition requires radiological adjudication, yet many trials have based case findings on coded diagnoses.
We investigated the feasibility of case finding through the existing coding system and reproducibility of radiological evaluation, in two hospitals in Israel. BP exposure of AF patients was compared to a control group with supratrochanteric fractures.
Computerized diagnoses 2007- 2010, were reviewed. X-rays of patients with suitable fracture location by ICD-9 codes were examined by two senior radiologists, in two steps. The fractures were classified as Atypical or Not-Atypical according to the published criteria. A 2:1 control group was created, matched by age and sex. Ambulatory drug acquisition data of AF and control patients was reviewed.
Both hospitals treated 3123 patients with hip fractures during the study period. One hundred-eighty-nine patients fulfilled the search criteria. Thirty-eight were classified by the first radiologist as compatible with AF. After the second crossover radiological opinion, 16 (42%) were judged as incompatible with the existing criteria. Complete BP acquisition data was available in 17 of the remaining 21 patients with AF, 15 (88%) of those were exposed to BP with average exposure length of 6.9 years, and drug compliance was over 80 %. Of those, 12 (80%) continued to receive BP for an average of 2.4 years after the AF. Only 1 AF patient was discharged with a suspicion of such a diagnosis. In a control group of 44 patients, only 14 (32%) were exposed to BP prior to fracture ($p<0.001$).
The relationship between AF and BP use begins with case identification. Lack of uniform code designation makes case identification difficult. Conclusions drawn from trials based solely on coded diagnoses might lead to a significant bias. Thorough radiological revision is mandatory for proper classification, and even when performed, inconsistency in interpretation does exist. BP exposure was significantly higher in AF patients, compared to the control group. Caregivers' unawareness of this unique entity might lead to improper management.

The Xa coagulation factor direct inhibitor rivaroxaban interferes with hormonal- induced physiological modulations in human female osteoblastic cell line SaOS2. (ID: 30)

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Background: The use of anticoagulants has been associated with systemic osteoporosis and increased risk for poor fracture healing but is inevitable following major orthopedic surgery of lower limbs. Rivaroxaban A (R) is an anticoagulant recently introduced in the clinical setting, which is a specific factor Xa inhibitor. We reported previously that R significantly inhibited cell growth, energy metabolism and alkaline phosphatase activity in human osteoblastic cell line $SaOS_2$, with no effect on mineralization, indicating transient interference with bone physiology.

Aim: We now investigated the effects of R on $SaOS_2$ response to osteoblast-modulating hormones.

Methods: $SaOS_2$ cell line was cultured and at sub-confluence treated with the different hormones and DNA synthesis (DNA), creatine kinase (CK) and alkaline phosphatase (ALP) specific activities were assessed. Also mRNA expression of estrogen receptor a (ERα), estrogen receptor b (ERβ), vitamin D receptor (VDR) and 25 Hydroxy- vitamin D_3- 1α hydroxylase (1OHase) mRNA was assessed by real time PCR.
Results: Treatments of $SaOS_2$ with: estradiol-17b (E_2), the phytoestrogens daidzein (D) and biochainin A (BA), the carboxy- pytoestrogenic derivative carboxy-D (cD), the ERa agonist PPT, the ERb agonist DPN, parathyroid hormone (PTH) and several vitamin D metabolites and analogs with/without R for 24h, resulted in significantly stimulated DNA, CK and ALP specific activities, but all these stimulations were totally inhibited when given together with R. R had no effect on mRNA expression of ERa, ERb, 1OHase and VDR, but inhibited hormonal modulations of mRNA expressions except this of VDR.

Conclusion: R inhibited significantly hormonal stimulation of different parameters indicating inhibition of not only the early stages of bone formation, but also the stimulatory effects of bone modulating hormones with a yet unclear mechanism. The relevance of these findings to human bone physiology is yet to be investigated.

Oral Presentations IV: GH, IGFs and Cancer

The transgenerational effects of weaning duration on gene expression in the neonatal rat liver (ID: 85)

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We have shown that the length of weaning in rats affects growth, development and metabolism, and that some of these effects are transgenerational. Rats weaned early (d16 vs normally at d21, or late at d26) developed to longer individuals with lower BMI, earlier key developmental events and reproductive maturation, and faster glucose clearance. In subsequent generations, the off-spring of late-weaned fathers but not mothers, were born lighter and were leaner at d10, but as adults, they were shorter with higher BMIs. These findings confirm previous reports of transgenerational effects of paternal nutrition, and further indicate that the duration of weaning affects both metabolism and the timing of various developmental and reproductive cues, involving epigenetic mechanisms.
The current study aimed to reveal genes that might be involved in this transgenerational effect on metabolism, by comparing gene expression on d1 in livers from off-spring of early- and late-weaned parents, using Affymetrix exon microarrays (n=3-4).
A total of 89 probe sets were differentially expressed ($P<0.005$) between groups. The corresponding analysis for enriched Gene Ontology terms and pathways clearly distinguished between the groups and indicated significant divergence ($P < 0.001$) in ROR-, PPARα-, PXR- and GR-activated pathways. Notably, mRNA levels for two genes were clearly higher ($P<0.005$) in off-spring of late-weaned parents: Major facilitator superfamily domain-containing protein 2a (MFSD2A) and P450 (cytochrome) oxidoreductase (POR). MFSD2A plays crucial roles in body growth and lipid metabolism and is nutritionally-regulated, increasing with fasting and decreasing upon refeeding. Its low levels are associated with elevated energy-expenditure, possibly explaining the leaner phenotype of the off-spring of early-weaned parents. POR regulates a large number of enzymes in the cytochrome P450 family, and thus has wide-spread effects, including in the regulation of retinoic acid levels during early embryonic development.
This complexity confounds interpretation of our data, but POR was previously shown to be reduced in off-spring of fathers on a low-protein diet, which displayed up-regulation of lipid and cholesterol biosynthetic pathways. MFSD2A and POR are both regulated by PPARα whose enhancer is methylated in inverse correlation with its expression levels, indicating a possible mechanism for the transgenerational inheritance in these animals.

Investigating new therapeutic strategies targeting hyperinsulinemia's mitogenic effects in a female mouse breast cancer model (ID: 5)

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Epidemiological and experimental studies have identified hyperinsulinemia as an important risk factor for breast cancer induction and for the poor prognosis in breast cancer patients with obesity and Type 2 diabetes. Recently it was demonstrated that both the insulin receptor (IR) and the insulin-like growth factor-I receptor (IGF-IR) mediate hyperinsulinemia's mitogenic effect in several breast cancer models. Whereas IGF-IR has been intensively investigated, and anti-IGF-IR therapies are now in advanced clinical trials, the role of the IR in mediating hyperinsulinemia's mitogenic effect remains to be clarified. Here we aimed to explore the potential of IR inhibition compared to dual IR/IGF-IR blockade on breast tumor growth.

To initiate breast tumors, we have inoculated the mammary carcinoma Mvt-1 cell line into the inguinal mammary fat pad (#4) of the hyperinsulinemic MKR female mice, and to study the role of IR we treated the mice bearing tumors with the recently reported high-affinity IR antagonist-S961, in addition to the well documented IGF-IR inhibitor picropodophyllin (PPP). While reducing IR activation, with resultant severe hyperglycemia and hyperinsulinemia, S961 treated mice had significantly larger tumors compared to the vehicle treated group. This effect may be secondary to the severe hyperinsulinemia mediated via the IGF-1 receptor. In contrast, PPP by partially inhibiting both IR and IGF-IR activity reduced tumor growth rate with only mildly metabolic consequences.
We conclude that have targeting (even partially) both IR and IGF-IRs impairs hyperinsulinemia effects in breast tumor development while simultaneously sparing the metabolic abnormalities observed when targeting IR alone with virtual complete inhibition.

Carotenoid derivatives inhibit the deleterious NFkB activity in bone and cancer cells by affecting strategic thiol groups (ID: 19)

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Background: Activation of the NFkB transcription system contributes to cancer progression, and has a harmful effect on bone health. Under un-stimulated conditions, the NFkB transcription factor is retained in the cytoplasm by the inhibitory protein IkB. Phosphorylation of IkB by IkB kinase (IKK) activates the system. Importantly, both IKK and the NFkB subunits, contain cysteine residues that are critical for their activity. The interaction of various electrophiles with these cysteines results in inhibition of NFkB. Intact carotenoids lack such electrophilic groups and we have recently demonstrated that carotenoid derivatives inhibit NFKB activity.

Aim: The aim of the current study was to determine the molecular mechanisms of this inhibition.

Results: We analyzed the structure-activity relationship of a series of dialdehyde carotenoid derivatives in NFkB inhibition. These compounds inhibited NFkB-driven reporter gene expression as well as several stages of the pathway in both cancer and bone cells. Moreover, the activity of the carotenoid derivatives depended on the reactivity of the electrophilic group in reactions such as Michael addition to SH groups in proteins. Specifically, carotenoid derivatives directly affected the NFkB machinery at two stages: the key regulatory enzyme IKK, as well as the p65 subunit of the transcription factor. Direct interaction with IKKβ was found in acellular in vitro kinase assay with a recombinant enzyme. Inhibition of p65 transcriptional activity was found in a reporter gene assay conducted in the presence of excess p65. A reducing agent partly reversed this effect. Inhibition of p65 activity at least partially results from reduced binding to DNA as evident from EMSA experiments. Interestingly, the binding of a mutant p65 where cysteine 38 was converted to serine was not affected by the derivative, proving that the interaction with this specific cysteine is crucial for the inhibitory ability of carotenoid derivatives. The same trend was observed with a cysteine-mutant of IKK.

In conclusion, we suggest that electrophilic carotenoid derivatives contribute to cancer prevention as well as bone health maintenance by inhibition of the NFkB transcription system. Strategic thiol groups of both IKK and p65 play a pivotal role in this process.

The involvement of miRNAs in mammary tumor growth and metastasis formation associated with hypercholesterolemia (ID: 4)

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Dyslipidemia has been associated with an increased risk for developing breast cancer. We previously demonstrated that a hypercholestrolemic environment in the apolipoprotein E knockout mouse model (apoE-/-) is a favorable setting for mammary tumor cell proliferation and metastasis to the lungs. However, the molecular mechanisms are still unknown. To unravel the molecular mechanism involved in enhanced tumor growth in apoE-/- mice, we have studied the response of MVT-1 cells to cholesterol in vitro. We found that cholesterol increased Akt phosphorylation s and cellular proliferation in MVT-1 cells. Several studies have shown that MicroRNAs (miRNAs), play an important role as tumor suppressors or oncogenes in breast cancer. Thus, tumor formation and metastasis are affected by the regulation of the miRNAs.

In this study we set out to identify the involvement of miRNAs in mammary tumor growth associated with hypercholesterolemia. We chose several candidate miRNAs, which play an important role in the development or progression of breast cancer. We found that there is a significant increase in miR-9, miR-221 ($P<0.005$), and in miR 21 ($P<0.05$), in breast cancer tumors from apoE-/- mice compared to control mice, suggesting that hypercholesterolemia may promote mammary tumor growth by elevating the expression of the prometastatic miRNAs. Surprisingly, we found an increase in miR-16 expression in apoE-/- mice compared to control mice, which is known as tumor suppressor in multiple types of cancer, including breast cancer. Our continuous investigation on miR-9 target genes have shown a significant increase of vimentin's mRNA level, known as intermediate filament protein that is expressed in mesenchymal cells, in apoE-/- mice.

Collectively we suggest that hypercholesterolemia in apoE-/- mice may enhance the growth of mammary tumors by elevating of specific oncogenic and prometastaic miRNAs, which in turn mediate upregulation of markers of epithelial-mesenchymal transition, like vimentin.

The effects of the autophagy inhibitors hydroxychloroquine and chloroquine, alone or in combination with the mTOR inhibitors Everolimus and Torin1, on neuroendocrine tumor cells (ID: 24)

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Background: Neuroendocrine tumors (NETs) constitute a heterogeneous family of neoplasms. Curative excision is usually possible only in a small group of patients, most of these patients require systemic treatment, the efficacy of which is extremely limited. Everolimus (RAD001) and Torin1 are mTOR inhibitors known to interfere with cell proliferation in NETs. However, cancer cells may use autophagy to counteract chemotherapy toxicity and prolong survival. Hydroxychloroquine (HCQ) and its derivative Chloroquine (CQ) have been shown to inhibit autophagy.

Aim: To explore the mechanisms of autophagy inhibitors alone or in combination with mTOR inhibitors on NET cells proliferation and autophagy process.

Methods: Cultured human NET cell line BON-1 was treated with RAD001, Torin1, HCQ and CQ alone or in combinations. Cell viability was tested using XTT assay. Flow cytometry and Western blot analysis were used to assess drug effect on cell cycle, apoptosis, PI3K/Akt/mTOR and autophagy pathways.

Results: RAD001 reduced cell viability by 20%, while HCQ and CQ suppressed cells viability up to 65% and 80% respectively. Torin1 significantly decreased cell viability (up to 55%). The addition of RAD001 to HCQ or CQ did not increase the inhibitory effect of either drug given alone. The combination of Torin1 with either HCQ or CQ significantly reduced cell viability (up to 83-90% and 90-97%, respectively) compared to each drug alone. RAD001 in combinations with HCQ and CQ mildly increased cell-cycle arrest in G0/G1 (74% and 78% vs. 69% in untreated cells). However, Torin1 significantly arrested cells in G0/G1, both alone (72%) as well as in combination with HCQ or CQ (81% and 73% respectively).

Conclusion: The combination of the global mTOR inhibitor Torin1 with the autophagy inhibitors HCQ or CQ seems promising for the inhibition of cell proliferation in this neuroendocrine tumor cell model.

The acromegaly gene expression signature in human adipose tissue reveals possible new mechanisms for enhanced lipolysis and insulin resistance (ID: 14)

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Context: Growth hormone has clinically important effects on adipose tissue, including stimulation of lipolysis and lipid oxidation, enhancing of lipoprotein lipase (LPL), increase in UCP3, inhibition of adiponectin, inhibition of conversion of cortisone to cortisol and decrease in insulin sensitivity. Patients with acromegaly have impaired insulin sensitivity and increased lipolysis.

Aim: The objective of this study was to determine the effect of chronic excess growth hormone in acromegaly on gene expression in adipose tissue in humans.

Experimental design: We compared global gene expression in subcutaneous fat biopsies from acromegaly patients undergoing transsphenoidal pituitary adenomectomy with that of controls undergoing a similar surgery for non-functioning pituitary adenoma. The patients underwent pre-operative clinical and metabolic profiling including assessment of HOMA-IR. Explants of adipose tissue from patients were assayed ex-vivo for lipolysis. mRNA was analysed by next-generation sequencing and bioinformatic analysis of transcript expression was performed.

Results: We observed enhanced ex vivo lipolysis in adipose tissue explants from acromegaly patients, consistent with over a 6 fold induction in beta adrenergic receptor-3 expression and LPL expression that was 2 fold higher compared to controls. Interestingly, TSH-R expression was induced 6 fold, possibly contributing to induction of lipolysis. Expression of TCF7L2, a diabetes susceptibility gene whose expression in adipose tissue has been correlated with diabetes, was higher in acromegaly patients,, and could possibly be a factor in the growth-hormone-induced insulin resistance. 11β-hydroxysteroid dehydrogenase type 1 expression was 4 fold lower in acromegaly patients. As expected, adipose tissue IGF-1 and IGF-BP3 expression was higher (3.7 fold and 2.4 respectively), in acromegaly patients. Bioinformatic analysis identified over a hundred additional differentially expressed genes and transcripts in adipose tissue of acromegaly subjects compared to controls, including gene clusters for growth, lipid metabolism, energy homeostasis and apoptosis.

Conclusions: We have identified the acromegaly gene expression signature in human adipose tissue. The significance of altered expression of TCF7L2, beta adrenergic receptor-3 and TSH-R genes to the insulin resistance and enhanced lipolysis in acromegaly will enhance our understanding of the metabolic changes in fat tissue which are associated with acromegaly.

Initiation of growth hormone therapy in idiopathic short stature: do gender differences exist? (ID: 92)

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Background: Growth hormone (GH) registries indicate that boys receive preferential GH treatment for idiopathic short stature (ISS). However, data comparing the clinical characteristics of boys and girls at initiation of treatment remain scarce.

Objective: To determine whether age, pubertal status and auxological parameters differ between genders at initiation of GH therapy for ISS.

Patients and Methods: Review of the computerized files of the endocrine department in a tertiary pediatric medical center identified 184 patients who started GH therapy for ISS in 2003-2011. Data on auxological parameters, predicted height, and parental height were collected and compared between boys and girls.

Results: Boys accounted for a significantly higher percentage of the study group (n=121, 65.8%) than girls ($p<0.001$). At onset of GH therapy, there were no significant differences between boys and girls in age (10.2±3.1 vs. 9.9±2.4 years, p=0.517), height-standard deviation score (SDS)(-2.64±0.5 vs. -2.79±0.5, p=0.07), body mass index-SDS (-0.65±1.01 vs. -0.80±1.13, p=0.349), or pubertal status (66% vs. 63.5% prepubertal, p=0.917). Predicted height-SDS was significantly higher among boys than girls (-1.48±1.01 vs. -2.22±0.75, $p<0.001$). Target height SDS(-1.10±0.77 vs. -1.01±0.08, p=0.482) as well as paternal (169.5±7.7 vs. 169.7±7.8, p=0.889) and maternal (155.4±6.3 vs. 156.9±6.2, p=0.112) stature were also similar in boys and girls.

Conclusions: Despite the male predominance among patients treated with GH for ISS, there appear to be no gender differences in auxological characteristics at initiation of therapy. The present study shows that male and female patients with ISS start therapy at the same age, with a similar height deficit, pubertal status, and target height.

Oral Presentations V: Reproduction and Puberty

The diagnostic value of first-voided urinary LH compared with GnRH-stimulated gonadotropins in differentiating slowly-progressive from rapidly progressive-precocious puberty in girls (ID: 13)

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Objective: Characterization of pubertal progression is required to prevent unnecessary intervention in unsustained or slowly-progressive (SP) precocious puberty (PP) while delivering hormonal suppression in rapidly-progressive (RP) PP. We aimed to assess the diagnostic value of first-voided urinary LH (ULH) compared with GnRH-stimulated gonadotropins in differentiating these forms of PP.

Methods: 62 girls with PP underwent both GnRH stimulation and ULH assay. Fifteen girls with peak LH>10 IU/L (i.e. advanced puberty) started treatment immediately whereas other 47 girls were evaluated after 6 months for pubertal advancement, height acceleration and bone-age progression. Based on these criteria, the participants were assigned to 5 subgroups: pubertal regression, no progression, or progression by one, two or three criteria. The first three subgroups were defines as SP-PP (n=29) while the other subgroups (including advanced puberty) were defined as RP-PP (n=33). Additional 23 prepubertal girls were evaluated for ULH.

Results: ULH but not serum gonadotropins could distinguish girls with two and three criteria from less progressive subgroups. By comparison to SP-PP, those with RP-PP had higher basal (0.81±1.43 vs. 0.12±0.05 IU/L, p=0.003) and peak LH (10.90±10.09 vs. 2.78±1.78 IU/L, p<0.001), basal FSH (2.60±2.07 vs. 1.17±0.89, p<0.001), peak LH/FSH ratio (0.98±0.76 vs. 0.22±0.12, p<0.001) and ULH (2.68±1.83 vs. 1.05±0.26 IU/L, p<0.001). Based on ROC analysis, a ULH cutoff of 1.15 IU/L has a better sensitivity (91%) and negative predictive value (88%) than other parameters, with specificity and positive predictive value of 72% and 79%, respectively.

Conclusion: ULH assay is a non-invasive, reliable method that can assist in the distinction between SP and RP-PP.

The Hypothalamic-Pituitary-Gonadal (HPG) axis is active in infants with Prader-Willi Syndrome (PWS) (ID: 53)

Harry Hirsch *Shaare Zedek Medical Center, Talia Eldar-Geva, Shaare Zedek Medical Center, Varda Gross-Tsur, Shaare Zedek Medical Cente.*

Background: "Mini-puberty" refers to transient activation of the HPG axis with increased levels of LH, FSH, and gonadal hormones during the first few months in normal infants. By contrast, hormone levels remain low in infants with hypogonadism due to congenital hypothalamic-pituitary defects. "Mini-puberty" has been described in several PWS male infants, but hormonal profiles in PWS female infants have not been reported.

Objectives: Measure gonadotropin and gonadal hormone levels in PWS male and female infants and assess gender-specific patterns of hormone secretion.

Methods: Blood samples were obtained from 12 (6 M, 6 F) infants with PWS ages 1 – 4 months. The genetic diagnoses for M:F were deletion in 5:4 and UPD in 1:2. Gestational ages (mean±SD) were 39±3 weeks (M) and 39±2 weeks (F). Birthweights were 2.58±0.54 kg (M) and 2.71±0.51 (F). Infant hormone levels were compared with values in 9 prepubertal PWS boys (2–10years) and 13 PWS girls (2–7years). Lower limits of assay sensitivities for testosterone, estradiol, inhibin B, and anti-Mullerian hormone (AMH) were 0.35 nmol/l, 37 pmol/l, 10 pg/ml, and 0.017 ng/ml. The Mann-Whitney U test was used for statistical analyses.

Results: Hormone levels for PWS infants were in the normal ranges for age. LH/FSH ratios were significantly higher in boys than in girls: 0.70±0.52 vs 0.19±0.15, p =.037. Testosterone was 4.01 (2.98 – 5.69) nmol/l in boys. Estradiol was detectable in 3 infant girls (39, 46, and 81 pmol/l). AMH was 93.9 (44.9 – 156.9) ng/ml in boys and 1.9 (0.1 – 7.9) ng/ml in girls, p=.004. Inhibin B levels were 141, 188, and 325 pg/ml in three boys, but levels were undetectable all female infants. Levels of LH, FSH, testosterone, AMH, and inhibin B were all significantly higher in infant boys compared to levels seen in prepubertal PWS boys ages 2 to 10 years (p=.001,.002,.001,.007,.003, respectively). In female infants, only FSH was significantly elevated compared to prepubertal levels (p = 0.04).

Conclusions: The HPG axis is active in male and female PWS infants. Hypogonadism in PWS cannot be attributed to congenital gonadotropin deficiency.

Treated and untreated women with idiopathic precocious puberty in the 3rd and 4th decades - long-term follow-up and reproductive outcome (ID: 59)

Elected as best clinical abstract

Yael Lebenthal, *The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Joseph Meyerovitch, The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Liat de Vries, Schneider Children's Medical Center, Moshe Phillip, Liora Lazar, Schneider children medical center.*

CONTEXT: Central precocious puberty (CPP) due to premature activation of the hypothalamic-pituitary-gonadal axis may affect the reproductive competence, educational achievements and social adaptation in adulthood.

OBJECTIVE: To assess the reproductive function and psychosocial adjustment of gonadotropin-suppressive–treated and untreated CPP women in the 3rd and 4th decade of life.

DESIGN: Prospective study of historical cohort.

SETTING: Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel (SCMCI).

PATIENTS: Study group - 214 CPP women aged 25-56 years were categorized into 3 groups: 135 GnRHa-treated, 18 CyA-treated, 61 untreated. Control group – 446 women with normal puberty from the SCMCI staff, matched for age and year of birth.

METHODS: Demographic data and gynecological status were recorded by researchers in a structured phone interview of the study group and a face-to-face interview of the controls.

MAIN OUTCOME MEASURES: Polycystic ovary syndrome (PCOS) and signs of hyperandrogenism, fertility and reproductive function, educational and marital status.

RESULTS: Median time to interview from endocrine discharge was 17.1 years (12.5-35.6). PCOS was more frequent in CPP women than in controls: GnRHa-treated 29.6% vs. 17.4% (p=0.006), CyA-treated 50% vs. 20.4% (p=0.04), untreated 35.4% vs. 17.2% (p=0.0003), with no significant difference between CPP groups. Spontaneous pregnancy was similarly achieved by treated-CPP and controls: GnRHa-treated 90.4% vs. 93.4%, CyA-treated 86.7% vs. 90.2%. Assisted fertilization rate was significantly higher in untreated-CPP than treated-CPP groups (p=0.006) and controls (p=0.03). The only parameter associated with PCOS and fertility problems was untreated CPP (OR= 2.04, 95% CI, 1.0–4.16, p=0.07 and OR= 3.40, 95% CI, 1.15–10.0, p=0.047, respectively). Course of pregnancy was uneventful in 90.2% of CPP women and 90.9% of controls. Marital status, education, pregnancy rate, and number of children were similar in CPP women and controls.

CONCLUSIONS: The increased rate of PCOS among former CPP women implies that the underlying neuroendocrine dysfunction manifesting as CPP persists into adult life and predisposes to reproductive disorders. Gonadotropin-suppressive therapy may have a protective effect on the reproductive outcome as fertility problems were more prevalent only among untreated-CPP women. Educational achievements and social adaptation in adulthood were unaffected by CPP.

Dentritic cells - new players in ovulation (ID: 11)

Adva Cohen-Fredarow*, Tal Raz, Ari Tadmor, Naama Meterani, Nava Nevo, Gil Mor, Michal Neeman, Nava Dekel*

The suggested analogy between ovulation and an inflammatory response takes into account the fact that during ovulation follicles become hyperemic, produce prostaglandins and synthesize a hyaluronan-rich extracellular matrix. This idea goes along with the preovulatory LH-induced upregulation of inflammatory-associated genes, increase in vascular permeability and invasion of immune cells into the ovary.
We hypothesized that these immune cells, specifically dendritic cells (DCs), play a role in ovulation and corpus luteum formation.
To examine modifications in DCs abundance and determine their localization we used transgenic mice, in which the expression of the DCs marker, CD11c is conjugated to YFP. In order to find their origin we transplanted WT ovaries under the kidneys capsule of YFP-CD11c transgenic hosts mice. For conditional ablation of these cells, we injected diphtheria toxin into transgenic female mice, in which the expression of simian diphtheria toxin receptor is under the control of the CD11c promoter. We found that CD11c positive- F4/80 negative-cells, apparently DCs reside in the ovary prior to ovulation. As the ovulatory process progresses, DCs are recruitment from the blood circulation and massively accumulate in the newly formed corpus luteum. We further revealed that CD11c positive cells are absolutely essential for expansion of the cumulus oocytes complex, the release of the ovum from the ovarian follicle, as well as for the formation of a functional corpus luteum. We also demonstrated that these effects of CD11c positive cells are mediated by upregulation of ovulation-essential genes and stimulation of lymphangiogenesis. Unexpectedly, we detected a remarkable anti-inflammatory capacity of the CD11c positive cells, which seemingly serves to restrict the ovulatory-associated inflammatory response.
Our results provide strong evidence for the involvement of DCs in controlling the ovulatory response.

Elucidation of the ubiquitin-proteasome pathway during the first meiotic division (ID: 10)

Inbal Kirenberg Ben-Eliezer, *Yael Pomerantz, Dalia Galiani, Nava Nevo, Nava Dekel*

Meiosis in oocytes is a complex process that involves a large variety of control elements. A key regulator of meiosis is cyclin-dependent kinase 1, the activity of which is determined by the availability of cyclin B1. Cellular levels of cyclin B1 are modified in a cycling manner and its degradation is executed by the ubiquitin-dependent proteolysis machinery. Decoration of protein substrates by a ubiquitin chain that tags it for proteasomal degradation, consists of three sequential steps facilitated by multiple enzymes E1, E2 and E3. Our present study aimed at deciphering the specific ubiquitin-conjugating enzymes (E2s) that play a role in this system. For that purpose, we either depleted or over-expressed different E2 proteins, by microinjecting mouse oocytes with specific morpholino antisense for interference with the translation of the corresponding E2 mRNAs or with cRNA of these E2s, respectively. The microinjected oocytes were allowed to resume meiosis in vitro and microscopically monitored for the extrusion of the first polar body (PBI). These examinations were complemented by live imaging analysis.

We found that the extrusion of PBI was inhibited and that spindle formation and chromosome segregation were disturbed, by knocking-down of three E2 proteins, UBE2C, UBE2S and UBE2D3. However, when UBE2C or UBE2S were over-expressed, the PBI formed earlier and in a higher oocyte fraction than in the control. Oocytes over-expressing these E2s also showed abnormalities in cell division as they did not arrest at metaphase II, but extruded the second PB. In conclusion, our study identified and characterized the E2 proteins that participate in the ubiquitination process during meiosis.

The results of this project shed light on the complexity of meiosis. Identification of the factors that participate in appropriate chromosome segregation and their characterization may contribute to our understanding of unfaithful chromosome segregation.

Differential dopaminergic effects on LH and FSH in a teleost (ID: 96)

Matan Golan, *Hebrew University of Jerusalem, Jakob Biran, Hebrew University of Jerusalem, John Mapunda, Hebrew University of Jerusalem, Berta Levavi-Sivan, Hebrew University of Jerusalem*

The inhibitory effect of dopamine on LH secretion in teleosts is well documented while studies on the dopaminergic effect on FSH are scarce.
In the current study we examined the expression of the dopamine D2 receptor (DRD2) in gonadotrophs and the dopaminergic effect on gonadotropin secretion in adult tilapia (Oreochromis niloticus). In vitro studies on dispersed pituitary cells revealed that while all three native forms of GnRH elicit FSH and LH release, the D2 receptor agonist quinpirole inhibits LH, but not FSH secretion. When applied in vivo, quinpirole was very potent in inhibiting the secretion of LH but did not affect plasma levels of FSH, both in the presence or absence of GnRH. Metoclopramide, a dopamine D2 antagonist, elevated LH plasma levels and enhanced the response of LH to GnRH but had no effect on FSH secretion. Finally, using a combination of in situ hybridization and immunofluorescence we investigated the expression of DRD2 in gonadotrophs of mature tilapia. Confocal microscopy analysis revealed DRD2 to be widely expressed in LH cells, however, we could not identify dopamine receptor expression in FSH gonadotrophs.
Taken together, these results suggest that the role of dopamine in the regulation of FSH is negligible in comparison to its effect on LH, probably due to decreased expression of the DRD2 receptor in FSH gonadotrophs.

LH and hypoxia acting via HIF-1α cooperate in Endothelin-2 expression (ID: 17)

***Ronit Yalu**, Adepeju Oyesiji, **Hebrew University Of Jerusalem**, Eyal Klipper, Rina Meidan.*

Hypoxic conditions prevail in the newly formed corpus luteum (CL) since the angiogenic process lags behind the intense luteal cell proliferation. Hypoxia triggers expression of a select set of genes that participate in angiogenesis, cell proliferation and survival. Physiological responses to hypoxia are mediated by Hypoxia-inducible factor-1α (HIF-1α) for oxygen homeostasis. Stabilized HIF-1α protein initiates transcription of target genes by transactivation of the hypoxia-response element (HRE) in their promoter. We have previously shown that endothelin-2 (EDN-2) is induced during CL formation in luteinizing granulosa cells (GCs). We aimed to characterize the effects of LH and hypoxia on the expression and up-regulation of EDN-2 and other hypoxia inducible genes (VEGF and glucose transporter-type1 -SLC2A1) and the role of HIF-1α in the process. Two cell models: primary bovine GC (bGC) and transformed human GC (SVOG) were examined using cobalt chloride ($CoCl_2$, a hypoxia mimicking agent) with or without LH or forskolin.

In SVOG, forskolin and $CoCl_2$ additively elevated levels of HIF-1α protein and EDN-2 mRNA. In bGC, LH alone elevated HIF-1α mRNA but not its protein, interestingly, LH with $CoCl_2$ synergistically collaborated to promote HIF-1α protein levels. LH and $CoCl_2$ each elevated mRNA of EDN-2, VEGF and SLC2A1 but an additive effect was evident when combined. To further establish the role of HIF-1α, we silenced its expression with specific small interfering RNA (siRNA). There was indeed a significant (85%) knockdown of the protein, this resulted in lower expression of EDN-2 and SLC2A1 mRNA as well as VEGF protein in SVOG treated with forskolin and $CoCl_2$. However, the siRNA was less efficient in silencing HIF-1α in bGC, so we opted to incubate the cells with inhibitors of HIF-1α (topotecan and 17AAG). As expected, these inhibitors decreased HIF-1α protein and simultaneously reduced EDN-2 mRNA, further illustrating the essential role of HIF-1α in its transcriptional regulation.

These results indicate that HIF-1α is an essential mediator of LH/forskolin and hypoxia for induction, expression and regulation of EDN-2. These findings may provide an explanation for the rise in the levels of these HIF-1α dependent genes in developing CL and suggest a role for EDN-2 during CL formation.

Posters

A map of poster location is found at the last page of the book

Posters: Bone, Vitamin D and Calcium Metabolism

P-41

Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. (ID: 28)

Marina Shargorodsky

Background and aims: Vitamin D supplementation has the potential to alleviate the cardiovascular damage in diabetic patients. The present study was designed to evaluate long term impact of high doses of vitamin D on arterial properties, glucose homeostasis, adiponectin and leptin in patients with type 2 diabetes mellitus.

Methods and Results: In randomized, placebo-controlled study 47 diabetic patients were assigned into two groups: Group 1 received oral daily supplementation with vitamin D at a dose of 1000 U/day for12 months. Group 2 received matching placebo capsules. Blood sampling for metabolic parameters, including fasting glucose, lipid profile, HbA1C, insulin, hs-CRP, 25 OH VitD, adiponectin and leptin was performed at baseline and at the end of the study. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR). Central aortic augmentation index (AI) was evaluated using SphygmoCor.

Results: The two groups were similar at baseline in terms of hemodynamic parameters. After 12 months, AI decreased significantly during the treatment period in patients received vitamin D ($p<0.0001$) and did not change in placebo group. Glucose homeostasis parameters, leptin as well as leptin adiponectin ratio did not change in both groups. 25 OH Vit D level significantly increased ($p=0.022$) and circulating adiponectin marginally increased ($p=0.065$) during 12 month treatment period in active treatment and did not change in placebo group.

Conclusions: High doses of vitamin D supplementation in diabetic patients was associated with significant decrease in AI during one year treatment. This beneficial vascular effect was not associated with improvement in glucose homeostasis parameters.

P-42

Vitamin D deficiency among physicians in Israel: a comparison between hospitalists and community based physicians. (ID: 34)

Noa Sylvetsky, *Shaare Zedek Medical Center, Gavriel Munter, Tamar Vineberg, Shaare Zedek Medical Center*

Background: Vitamin D deficiency is now recognized as a widespread phenomenon, even in Mediterranean countries such as Israel. In the past few years, there has been an increased awareness of a possible link between vitamin D deficiency and several diseases. Individuals at risk of Vitamin D deficiency include those with limited exposure to sunlight, low intake of dairy products, malabsorption and malnutrition. Experts suggest measurement of serum vitamin D in high risk individuals. Physicians may be vulnerable to low vitamin D levels due to the long work hours and lack of sun exposure.

Objective: To compare serum 25(OH) D levels between hospital based physicians and community-based physicians during the winter months.

Methods: 43 physicians who work at Shaare Zedek Medical Center in Jerusalem and 38 physicians who work in the community were recruited. Physicians' serum 25 (OH) D levels were measured and the physicians completed a questionnaire to assess the risk of vitamin D deficiency. The results were compared by means of independent T-test, Chi-Square test and Fisher's exact test.

Results: Mean serum levels of 25 (OH) D among hospitalist physicians were significantly lower than the mean serum levels of 25 (OH) D among community-based physicians. The vitamin D level within the hospital doctors was at 15± 6 ng/ml, in comparison with the level of vitamin D within the community-based physicians which was 19.7 ±6 ng/ml. ($p = 0.001$). 55.8% of hospital based doctors had less than 15 ng/ml compared to 26.3% of community physicians. The variables that were significantly linked to low mean serum levels of 25 (OH) D were: younger age, night shifts, daily sun exposure and ethnic origin.

Conclusion: Hospitalist physicians are at greater risk for low vitamin D levels than community-based physicians, and should be considered for screening and therapy.

P-43

Bone density and vitamin D status in liver transplant patients 10 years after the first assessment (ID: 38)

Elena Segal, *Rambam Health Care Campus, Yacov Baruch, Rambam Health Care Campys, Marina Nodelman, Rambam Health Care Campus, Rimma Kramskay, Rambam Health Care Campus, Marina Heifetz-Kustanovich, Sophia Ish-Shalom*

Background: Twelve years ago we evaluated 29 liver transplant patients. Nineteen (65.5%) had decreased bone mass, 11 (37.8%) were osteoporotic, 28 (96.5%) had serum level of 25(OH)D<20 ng/ml, mean 12.52±3.19, mean PTH 59.67±29.78 pg/ml. None was treated with calcium or vitamin D supplements, in spite of low calcium intake and low or suboptimal 25OHD serum level. The patients received letters containing the diagnosis and treatment recommendations.

Results: Now we re-evaluated patients' charts. Nineteen patients continued follow-up at the Liver Unit, 9 men, 10 postmenopausal women, aged 58.8±15.8. Ten patients died, none of them had fractures. Twelve fractures were reported following transplantation, 10 (83.3%) within the first year, 2 in the following years, both were traumatic. Second BMD results were available for 8 (42%) patients, two (25%) were osteoporotic, 6(75%) - osteopenic. 13 patients (68.4%) received 600 mg of elemental calcium, 400-1600 IU of vitamin D daily, 2 (10.5%) received bisphosphonates. Plasma PTH range was 32-71 pg/ml, mean 61.9±26.42, 25OHD range was 14-22, mean 24.72±9.49 ng/ml. P=0.68and p=0.003 respectively compared with the inital evaluation data: PTH 59.67±29.78 pg/ml, 25OHD 12.52±3.19 ng/ml.

Since the first evaluation, 20 new post liver transplant patients joined the Rambam Liver Unit. They were not evaluated in the Bone Metabolism Unit. According to the information retrieved from the patients' charts, 7 of them had BMD evaluation, one woman was in the osteoporotic range, 6 –osteopenic, PTH was 82.83±67.01 pg/ml, 25OHD was 23.95±8.7 ng/ml. Nine (45%) of them are treated with calcium and vitamin D,600 mg and 400-2000 IU, respectively, two are treated with oral bisphosphonates. No fractures were reported by these patients since the time of transplantation. In the whole group of post liver transplant patients PTH was 71.82±49.64 pg/ml, 25OHD 25.11±9.31ng/ml.

Cocnclusion: Standards of care for post-transplant patients in the Liver Unit and family medicine have been changed during past years, majority of liver transplant patients are treated with calcium and vitamin D supplementation and have improved vitamin D status and nutritional calcium status.

P-44

Gigantomastia and hypercalcemia in a pregnant woman with Myasthenia Gravis (ID: 64)

Orit Barenholz-Goultschin, *Benjamin Glaser, Roy Abel, Rivka Pollak-Dresner, Hadassah-Hebrew University Medical Center, Jerusalem*

Background: Gigantomastia is a rare condition previously described in association with autoimmune diseases, particularly with myasthenia gravis. In some cases there is accompanying hypercalcemia and a hormonal predisposing factor such as pregnancy is often present.

Clinical case: A 21 year old woman was admitted with vomiting, diarrhea and dehydration in the 13th week of her first pregnancy. She was diagnosed with myasthenia gravis at age 16 years and underwent thymectomy. Current medical treatment included monthly IVIG, azathioprine, and pyridostigmine. On physical examination she had remarkable gigantomastia with red, warm, edematous breasts. Laboratory work up revealed hypercalcemia (3.54 mmol/L), P=0.8 mmol/L (0.8-1.4), undetectable PTH, normal prolactin level for pregnancy and 25OHD$_3$ of 4 ng/ml. Serum PTH-rP was 6.4 pmol/L (<2.0 pmol/L). To correct the hypercalcemia, IV fluids and lasix were initiated. Subsequently, S.C. calcitonin (up to 200units/d) and bromocriptine (up to 15mg/d) were added until normocalcemia was achieved. Breast US and histopathology revealed massive edema with pseudoangiomatous stromal hyperplasia

The literature regarding pregnancy-associated gigantomastia and hypercalcemia is scarce. Bilateral mastectomy has been advocated and this option was presented to the patient as well as discontinuation of her pregnancy. However, the patient decided to continue the pregnancy. With treatment she remained normocalcemic throughout the entire pregnancy, and serial obstetric US examinations showed normal fetus development up to week 34. During the 3rd trimester iv fluids, lasix and calcitonin were gradually discontinued, and vitamin D (200units/day) was gradually initiated while serum calcium level remained normal.

Conclusion: To our knowledge, this is the first report of medical treatment for gigantomastia-associated hypercalcemia of pregnancy resulting in maternal normocalcemia and normal fetal development. While excessive PTHrP secretion is a plausible underlying mechanism for the hypercalcemia, PTHrP-mediated hypercalcemia of malignancy is usually unresponsive to calcitonin, raising the possibility of cytokine and inflammation-mediated hypercalcemia originating from the inflamed breast. Indeed, the breast as the source of the inflammatory process in autoimmune disease-associated gigantomastia was previously shown (JCEM 90(9): 5287-5294. Medical treatment should be considered in cases of gigantomastia and hypercalcemia. Mastectomy or termination of pregnancy may not be the only therapeutic options.

P-45

Results of secondary fracture prevention program in patients with severe osteoporosis in Rambam Health Care Campus (ID: 71)

Sophia Ish-Shalom, *Elena Segal, Rambam Health Care Campus, Marina Heifetz-Kustanovich, Marina Nodelman, Rambam Health Care Campus, Doron Norman, Rambam Health Care Campus*

Background: The risk of additional osteoporotic fractures in patients that underwent a fragility fractures is at least 6-fold higher than in age and gender matched adults. Treatment strategies should be directed to provide intensive fracture prevention treatment to patients with osteoporotic fractures.

A collaborative (ortopedics and bone metabolism) fracture prevention program for patients that were hospitalized with osteoporotic fractures was initiated in Rambam Health Care Campus in 2008. All patients that were hospitalized with fractures were offered fracture prevention treatment after surgical fracture repair.

Results: 1647 patients, aged median 78 (range 23-103), 1165 (71%) women aged 78 (33-100) and 482 (29%) men aged 77 (23-103) were enrolled in the program between 2008 – 2013. Proximal femoral fractures were sustained by 1115 (68%) of all patients: 769 (66%) of women and 346 (72%) of men. 256 (16%) of patients died during the study period, 152 (13%) of women and 104 (22%) of men, in hip fracture patients 123 (16%) of women and 89 (26%) of men. The relative risk (RR) of men to die after a hip fracture was 1.61 (95% CI 1.26-2.05) compared to women. The major predictors of death in women were greater age, number of medications, creatinine and lower albumin, in men, greater age, number of medications, and creatinine. 264 (23%) of all women and 10 (2%) of all men were treated for osteoporosis before admission and 171 (22%) of women with hip fractures and 6 (2%) of all men with hip fractures. After discharge 404 (35%) of all women and 42 (9%) of all men received treatment, of hip fracture patients, 247 (32%) of women and 31 (9%) of men received treatment. While no factors were related to increased likelihood of men being treated, women were more likely to be treated if they had any previous fractures, previous treatment, higher vitamin D or albumin, and lower creatinine. Treatments distribution in all patients was: 319(19.3%) received oral bisphosphonates, 73 (4.45%) IV bisphosphonates (Zoledronate), 2 (0.12%) pamidronate), 47 (2.87%) teriparatide, 5(0.31%) raloxifen.

Conclusions: We conclude that in spite of increasing rate of patients that were treated after an index fracture, the rate is still low.

P-46

Hypoparathyroidism and central diabetes insipidus: a search for the link (ID: 84)

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Objective: The association between hypoparathyroidism and central diabetes insipidus (CDI) is very rare. We report two siblings with hypoparathyroidism and CDI in one of them.

Case Report: Two siblings, a 9-yr-old boy and a 5-yr-old girl, presented with hypocalcemic seizure at the age of 2 yr and 2 months and 2 yr and 4 months, respectively. Treatment for their hypoparathyroidism was initiated with elemental calcium, alpha-D3 and magnesium citrate. At the age of 3 yr, the girl developed polyuria and polydipsia and was diagnosed with CDI, with good response to DDAVP treatment. No posterior bright spot was demonstrated on a brain MRI. No other pathological clinical manifestations or laboratory alterations were observed during follow-up for both siblings except for intermittent hypercalciuria when the serum calcium levels were below normal range. Family history was unremarkable, there was no consanguinity, and both parents had normal calcium levels. The father is of Iraqi and Egyptian origin and the mother is of Iranian and Romanian origin. Molecular analysis for the CaSR, PTH and GCMB genes were negative. Whole exome analyses found the autoimmune regulatory (AIRE) gene mutation, Y85C, which is characteristic for Jewish Iranians with autoimmune polyendocrine syndrome type 1 (APS1). The AIRE gene PCR confirmed the siblings to be homozygous, the parents to be carriers, and the younger sibling to carry the wild-type allele. No other symptoms or signs of APS1 developed during 5 years of follow-up. Renin and ACTH-stimulated cortisol levels were normal, and antibodies against adrenal, beta-cell, ovary, thyroid, pituitary, celiac and parietal cell were negative in the described siblings. Laboratory findings on anti-diuretic hormone antibodies are pending.

Conclusion: Central diabetes insipidus is a rare manifestation of APS1, especially in the pediatric population. APS1 should nevertheless be part of the differential diagnosis in children presenting with CDI. The finding of the AIRE mutation in Iraqi Jews is most probably due to the geographical proximity to Iran.

P-47

Parathyroid surgery: preoperative localization studies in correlation with the surgical outcome – seven years experience in a single medical center (ID: 90)

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Background: Parathyroidectomy for primary hyperparathyroidism is based on symptoms (nephrolithiasis, renal failure or osteoporosis) or clinical parameters. Localization studies (positive or negative) are not part of the considerations for or against surgical approach. The type of surgical procedure performed, minimally invasive parathyroidectomy (MIP) or exploration, is based on localization studies in combination with surgeon and patient's preferences.

Objectives: To correlate the surgical outcome with preoperative localization findings, surgical technique and symptomatology.

Methods: Medical records of 169 consecutive patients with primary hyperparathyroidism who underwent parathyroidectomy from 1/2005-12/2012 were retrospectively reviewed for parathyroid-related symptoms, preoperative localization studies, surgical technique, complications, and outcome.

Results: All patients (134F/35M, 59.6±13.5 years) had primary hyperparathyroidism. 26% were asymptomatic, 19.5% had nephrolithiasis, 10.1% renal insufficiency, and 43.8% osteoporosis. Preoperative calcium was 11.5±0.8 mg/dl, (normal 8.5-10.5), parathyroid hormone (PTH) was 179±120 pg/ml (normal 15-65), and vitamin D was 47.7±24.3 nmol/l (normal 75-250). 76% had matched ultrasound (US) and sestamibi scan localization studies, whereas 10.7% had positive sestamibi and 8.3% US only, 3.6% had negative and 1.8% mismatched localization studies. MIP was performed in 81% of the patients, yet, only 46% had local anesthesia. 87% of matched group and 89% of the sestamibi only group had MIP, whereas, 66% of the mismatched and 57% US only group. Overall, pathology was consistent with adenoma in 95%. Postoperative biochemical parameters were not different among the groups. Complications were more frequent after exploration: 15.6% had vocal cord paralysis and 12.5% had transient hypocalcemia. Preoperative studies matched postoperative findings in 93% of the matched group, 94% of sestamibi and 100% US positive only groups.

Conclusions: About 90% patients with primary hyperparathyroidism and matched US/sestamibi studies or sestamibi-only underwent MIP, but only one-fifth of negative localization group. MIP was performed less often (58%) in the US-only group. Half the patients who underwent MIP had general anesthesia. No differences were found in preoperative and postoperative biochemical parameters between the different preoperative localization groups. Further studies are needed to determine the clinical utility of preoperative US in patients with primary hyperparathyroidism and positive sestamibi scan.

P-48

Identifying the threshold for vitamin D deficiency in relation to health indicators (ID: 95)

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Background: Lack of sun exposure in the High-Tech workers who spend most daylight time indoors increases the risk of vitamin D deficiency in this healthy population. While recent evidences raise an association between vitamin D status and health indicators, the clinical threshold for this tendency is undefined.

Objectives: to explore the associations between vitamin D status and health indicators among healthy men.

Methods: Healthy employees were recruited from a periodical check-up clinic. Blood pressure, BMI and waist circumference were measured. Serum concentrations of 25(OH)D, PTH, fasting plasma Insulin (FPI), fasting plasma glucose (FPG), total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG), and high sensitive C- Reactive Protein (hs-CRP) were assessed in fasting blood sample. Results: 358 men, aged 48.8 ±10.2 were enrolled. Mean age was 48.8 ±10.2y, BMI 27.0±3.8 k/m^2 and 25(OH)D serum level of 22.1± 7.9 ng/l. Severe deficiency (25(OH)D<10 ng/ml), was shown among 4.2%, 36.3% were deficient (10<25(OH)D<20 ng/ml), 44.7% had insufficiency levels (20<25(OH)D<30) and 14.8% had sufficient levels (25(OH)D>30 ng/ml). Across the 4 levels of 25(OH)D, lower 25(OH)D levels were associated with higher BMI (P=0.005) and waist circumference (P<0.001). Higher 25(OH)D was associated with Lower levels of FPI, HOMA-IR, HOMA-β, and TG. Diastolic (DBP) and systolic blood pressure (SBP) and hs-CRP levels were negatively associated with 25(OH)D levels (P<0.001, P<0.003, P<0.03 respectively). In adjusted multiple regression models to predict health outcomes, levels of 25(OH)D explained up to 4% of the total variance. A curved linear association was found with FPI and Homa-IR with a significant spline knot at 11ng/ml. For hs-CRP a spline knot at 14ng/ml was shown, suggesting possible cutoffs for the attenuation of the association. TG, SBP and DBP had a straight linear association with 25(OH)D (r=-0.232 P<0.0001, r=-0.260 p<0.0001 respectively).

Conclusion: We showed an independent association between 25(OH)D and health indicators including FPI, HOMA-IR, blood pressure and CRP in healthy men. Future studies are required to address temporal relationships and to test the impact of vitamin D supplementation in a clinical trial.

P-49

Atypical fractures of the femoral shaft - is there thicker cortex present? (ID: 97)

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Background: Atypical femoral fractures (AF) have drawn much attention during the last years. Extensive research aimed to determine possible connection to prolonged bisphosphonate (BP) use has been done and distinctive morphologic pattern of AF was discussed. Some suggested that AF are accompanied by thick femoral cortex and correlation between the magnitude of cortical thickening and the length of BP exposure has been reported. During the last year, several investigators challenged the concept of shaft cortical thickening.

Methods: We looked at cortical width of patients with AF, compared to typical shaft fractures, in a retrospective cohort of patients with subtrochanteric fractures. BP exposure was evaluated in the two groups. Computerized database of discharge diagnoses 2007-2012 was reviewed. ICD-9 diagnoses compatible with fracture location below femoral neck were chosen. Patients younger than 50 years and those with major trauma were excluded. Admission femoral X-rays of patients with suitable fracture location were examined by senior radiologist. The fractures were classified as Atypical or Not-Atypical (NA) according to the published criteria. Total femoral diameter, lateral and medial cortex width were measured 15 cm below the highest point of the greater trochanter. Ambulatory BP acquisition data of AF and NA fracture patients was reviewed. Multivariate model adjusted for age and BP length of exposure was performed.

Results: 1814 patients were admitted with femoral fractures. Among the 37 femoral fractures X-rays suitable for measurements, we found 13 AF and 24 typical subtrochanteric. The ratio of lateral cortical width/total femoral shaft width (LC/TFS) did not differ between the groups and were 0.247+0.051 and 0.240+0.047, respectively ($p=0.66$). No difference in shaft cortical thickening was found after multivariate analysis. BP exposure was documented in the 83 % of AF, compared to 18 % of NA fracture patients ($p<0.001$).

Discussion: Our data shows that patients with AF do not have a thicker cortex, compared to typical subtrochanteric fracture patients. Since two other recently published reports on the subject did not support the cortical thickening hypothesis, it must be re-thought. This work further strengthened the relationship between BP exposure and AF.

P-50

Pseudohypoparathyroidism: clinical, molecular characteristics and long term follow-up (ID: 105)

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Background: Pseudohypoparathyroidism type Ia (PHP-Ia) is a rare heterogeneous genetic disorder characterized by a typical phenotypic trait defined as Albright's hereditary osteodystrophy, and resistance to the action of different hormones that activate the Gs-coupled pathway, due to mutations in the GNAS gene witch encodes the α subunit of the stimulatory G protein (Gsα),

Objective: to investigate the clinical, biochemical and molecular aspects in the course of time, in four girls with suspected PHP-Ia.

Results: the girls descended from two un-related arab-muslim families in north Israel, two twin sisters and two sisters. All the girls had brachydactily of varying degrees and obesity first noticed at 6 months to 8 years old. Two girls have round face and short stature. Three patients have mild mental retardation and only one patient suffers from sub cutaneous calcifications. The first endocrine compromise in all patients was TSH resistance diagnosed from birth to 7 years old. All had normal sized and positioned thyroid gland as imaged in US and technetium scanning. Two girls are Eltroxine treated. PTH resistance developed later in all patients, from 9 months to 9 years old, only one developed hypocalcemia. Patients 1,2 have hypogonadotrophic hypogonadism and patient also GH deficiency. GNAS sequencing detected a known missense mutation in exon number 9 in patients 1 and 2 (c.692 C>T, p.R231C), while a novel deletion spanning exon 7 to 13 was found by Multiplex Ligation

Phenotype	Family no. 1- twins		Family no. 2- sisters	
	Patient 1	Patient 2	Patient 3	Patient 4
Brachydactily	+	+	+	+
Obesity	+	+	+	+
Short stature	+	+	_	-
Mental retardation	+	+	+	_
Subcutaneous calcifications	_	_	_	+
TSH-R	+	+	+	+
PTH-R	+	+	+	+
GHRH-R	+	_	_	_
Gonadotropins-R	+	+	_	_
GNAS mutations	c.692C<T	c.692C<T	13-7del	13-7del

Probe Amplification (MLPA) in patients 3 and 4.

Conclusions: obesity in children can represent the first sign of PHP-Ia therefor it is important pediatricians be familiar with this rare syndrome. Molecular diagnosis is important for genetic familial counseling. The clinical course in the patients over the years deepens our knowledge in the syndrome pathophysiology and justifies long- term follow-up to diagnose further endocrine resistances that evolves in time.

P-1

The efficacy of using the Internet-based CareLink® therapy management system for diabetes in patients with type 1 diabetes (T1D) (ID: 6)

Shlomit Shalitin, *Tal Sakal Ben Ari, MIchal Yackobovitch -Gavan, Moshe Phillip*

Objective: To assess the efficacy of the web-based CareLink® therapy management system on metabolic control, patient's satisfaction (PS) and quality of life (QOL).

Methods: In a randomized-controlled trial, 70 patients with T1D (mean diabetes duration 6.4 ± 4.7 years), treated with CSII≥3 months, mean age 14.0±5.3 years, mean HbA1c level 8.68±0.68% were randomized to: an intervention group (n =36) and a control group (n=34). During a 4-month period, in the intervention group usage of the CareLink® was assisted by the diabetes team through at least monthly contact via internet, in which patients submitted their pump and glucose levels data, whereas subjects in the control group were instructed to submit monthly their blood glucose levels via fax/email and were instructed for treatment adjustments by the same team. In the next 4 months patients from both groups were instructed to use the system at home. HbA1c levels, PS and QOL questionnaires were assessed at baseline, at 4 and 8 months.

Results: After 4 months, HbA1c levels decreased compared to baseline (intervention group: 8.75±0.84% to 8.45±0.90%, p=0.013, control group: 8.65±0.57% to 8.37±0.73%, p=0.054). Patients in both groups that submitted data<3 times during each 4-month segment were classified as non-compliant. Only in the intervention group the difference in HbA1c levels after first 4 months between compliant and non-compliant patients was significant (8.17± 0.81% vs. 8.99±0.85%, p=0.017), with a significant decrease in HbA1c in the compliant group (p=0.006). After 8 months, in the control group compliant patients who used the Carelink® had a significant decrease in HbA1c level compared with baseline (p=0.018). No significant changes were found in PS or QOL scores during follow-up in both groups.

Conclusions: Use of the CareLink® system was associated with a significant improved glycemic control only in compliant patients, without a change in PS or QOL

P-2

New onset diabetes mellitus in elderly subjects: association between HbA1c levels, mortality and coronary revascularization (ID: 12)

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Objectives: New onset diabetes mellitus in elderly patients is associated with increased risk of diabetic complications and mortality. It is unknown whether glycemic control in this population influences the mortality risk.

Research design and methods: The present study was conducted using the computerized database of the Sharon-Shomron district of Clalit Health Services in Israel. Included in the study were subjects 65-years-old and above with new onset diabetes mellitus. The primary outcome measures were all-cause mortality and coronary revascularization procedures with either percutaneous coronary intervention or coronary artery bypass grafting.

Results: 2,994 participants were stratified into 4 groups according to their mean HbA1c levels during the follow up period [<6.5% (48mmol/mol), 6.5 %-6.99% (48-52mmol/mol), 7%-7.49% (53-57mmol/mol) and ≥7.5% (58mmol/mol)]. During a mean follow-up of 5.54±2.1 years, 1,173 (39.17%) participants died and 285 (9.51%) underwent coronary revascularization. An HbA1c level above 7.5% (58mmol/mol) was associated with a significantly increased all-cause mortality rate (HR 1.74, 95% confidence interval, 1.2-1.8 $p<0.0001$). This difference remained statistically significant following a multivariate model adjusted for the conventional cardiovascular risk factors and for the use of hypoglycemic agents and statins. Kaplan-Meier survival plots revealed lower survival rates in this group of patients. Coronary revascularization rates were highest among subjects with HbA1c 6.5%-6.99% (48-52mmol/mol) (HR 1.6, 95% confidence interval 1.01-2.4, $p<0.05$) and lowest in patients with HbA1c≥7.5% (58mmol/mol).

Conclusions: An HbA1c level above 7.5% (58mmol/mol) is associated with increased risk for all-cause mortality and with a lower revascularization rate in elderly patient with new onset diabetes mellitus.

P-3

Basal-bolus insulin versus sliding scale insulin in management of inpatients with type 2 diabetes: a prospective randomized controlled study. (ID: 20)

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Background: Evidence indicates that hyperglycemia is associated with increased morbidity and poorer outcomes in patients hospitalized in general medical or surgical wards. Few randomized trials thus far have focused on the best management of inpatients hyperglycemia in the non-intensive care unit setting. We compared the efficacy and safety of a basal-bolus insulin (BBI) regimen with that of sliding scale insulin (SSI) in patients hospitalized in internal medicine department in Haemek Medical Center, Afula.

Design and patients: One hundred and six patients were prospectively randomized to receive regular insulin four times a day according to sliding scale protocol based on glucose measurements (n=54) or glargine and glulisine (n=52), according to body weight and glucose measurements. The goal of the treatment in all patients was to maintain pre-meals glucose levels between 140-180mg/dL

Results: The mean blood glucose of the 106 patients at admission was 199.72±83.0mg/dl and did not differ between the two groups. Hba1c was also similar in both groups (8.71±2% and 8.26±2.08%, for BBI and SSI groups, respectively). The average blood glucose during hospital stay do not differ (192.05±43.39 vs. 197.21±45.09 mg/dl for BBI and SSI groups, respectively). There were no group differences in glucose level at discharge, length of hospitalization, and frequency of hypoglycemia. The mean insulin daily dose was significantly higher with the BBI regimen than with that of SSI treatment ($p<0.001$). No death was noted in any participant during hospitalization.

Conclusions: Both insulin regimens demonstrated similar efficacy and safety in non-critically-ill patients with type 2 diabetes hospitalized in internal medicine department.

P-4

Impaired decline in renal threshold for glucose during pregnancy - a possible novel mechanism for gestational diabetes mellitus (ID: 21)

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Hypothesis: The renal threshold for glucose (RTG) is determined by the nephron's reabsorptive capacity. Glucose is reabsorbed through sodium-coupled glucose cotransporters (SGLTs) in the proximal tubules. During pregnancy renal glucose reabsorptive capacity decreases, possibly, due to reduced glucose transporter expression. Our hypothesis is that inadequate decrease in RTG during pregnancy will make women more prone to develop gestational diabetes mellitus (GDM).

Methods: Pregnant women (n=40) who were referred to our center for oral glucose tolerance test (OGTT) were included in the analysis. Plasma glucose levels and urinary glucose excretion (UGE) were measured for 4 hours after 100 gr oral glucose load. These data was used to calculate RTG. The subjects were divided into two cohorts, GDM and non-GDM, according to the OGTT results. Mean RTG was compared between the two groups.

Results: Fifteen (37.5%) of the women were diagnosed with GDM. Seventeen participants had only trace amounts of UGE and no value of RTG could be determined, RTG was determined in the other 23 subjects. Among these 23 women, 13 were diagnosed as GDM and 10 had normal OGTT. RTG was lower in the non-GDM women (146 ±14 mg/dl) than in the GDM women (182±18 mg/dl), $p< 0.001$.

Conclusions: GDM is associated with higher RTG during pregnancy compared with non-GDM. These results support our hypothesis that inadequate decrease of the RTG may have a pathophysiological role in the development of GDM.

P-5

Do adiponectin levels explain the atherogenic properties of Hp 2-2 phenotype in type 2 diabetic patients? (ID: 29)

Marina Shargorodsky

Objectives: Haptoglobin (Hb) and adiponectin are antioxidant proteins and independent predictors of atherosclerotic vascular disease in diabetic patients. The link between Hp phenotype and circulating adiponectin levels were examined.

Methods: Diabetic patients were divided into two groups by Hp phenotype: Hp 2-2 group and non-Hp 2–2 group (Hp2-1 and Hp 1-1). Blood glucose, HbA1C, insulin, lipids, CRP, HOMA-IR, 25OH vitamin D, leptin and adiponectin levels were measured. Pulse wave velocity (PWV) was performed using SphygmoCor (version 7.1, AtCor Medical, Sydney, Australia).

Results: PWV was significantly higher in patients homozygous for the 2 allele (Hp 2-2) compared to non-Hp 2–2 patients (Hp 1-1 and Hp 1-2), $p<0.0001$. Adiponectin was significantly lower in Hp2-2 patients than in non-Hp 2–2 group ($p<0.016$). Neither leptin nor the leptin adiponectin ratio (LAR) differed significantly between groups.

Conclusions: PWV was significantly higher and plasma adiponectin levels were significantly lower in diabetic patients homozygous for the 2 allele (Hp 2-2). These differences were detected despite the lack of by-phenotype differences in glycemic control, blood pressure level or presence of cardiovascular risk factor and suggest an active role of adiponectin in the pathophysiology of vascular disease in this population.

P-6

Long duration of hyperglycemia in the first 96 hours of life is associated with severe intraventricular hemorrhage in preterm infants (ID: 51)

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Background: Fluctuations in blood glucose levels affect blood osmolarity, cerebral blood flow and brain metabolism – possibly contributing to the development of intraventricular hemorrhage (IVH) in preterm infants. We aimed to assess the possible association between severe IVH and blood glucose parameters during the first 96 hours of life in preterm infants.

Methods: Preterm infants with IVH grade 3-4 (n=70) were compared to matched infants with similar gestational age and birth weight, but with no IVH (n=108). Studied parameters included the frequency and duration of hyper/hypoglycemic (>6.9/ <3.3 mmol/L, respectively) events, the extreme slope of an event evolution, the maximal glucose value observed and the "hyper/hypoglycemic index" representing a weighted average of the hyper/hypoglycemic amplitude.

Results: The IVH group had significantly more hyperglycemic events (2.9 ± 1.7 vs. 2.4±1.8 events, $p<0.05$) with longer duration (22.2±14.2 vs. 14.1±12.5 hours, $p<0.001$) and a higher hyperglycemic index (25.9±18.8 vs. 17.7±16.2 mmol/L, $p=0.003$) when compared with the non-IVH controls. Respiratory distress syndrome, hypotension and thrombocytopenia increased the adjusted odds ratio for IVH. Surprisingly, hypoglycemia and extreme changes in blood glucose levels were not independently associated with IVH. Conversely, the increase in even mild hyperglycemic duration was most prominently increasing the adjusted odds ratio for severe IVH (Odds Ratio=10.33!, 95% CI= 10.0-10.6, p= 0.033).

Conclusion: Longer duration of hyperglycemia in the first 96h of life is strongly associated with severe IVH in preterm infants. Consequently, interventional studies aiming to determine the selective effect of continuous control of long lasting hyperglycemia by appropriate and timed insulin treatment on the incidence of severe IVH are warranted.

P-7

Obesity is associated with lower basal state cortisol, and diminished cortisol response to the low dose 1ug ACTH: time to depart from the obesity/pseudo-Cushing myth (ID: 60)

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Background: Obesity can resemble Cushing's syndrome not only with respect to some clinical and biochemical features such as visceral adiposity, hypertension and metabolic abnormalities but also in terms of increased urinary excretion of cortisol and cortisol metabolites. This has subsequently led to some confusion regarding activity level of the hypothalamic-pituitary axis in obesity. Here we re-examined this question using several tools developed after the evolution of the concept of "pseudo-Cushing in obesity", namely, the measurement of serum free cortisol, salivary cortisol and the dynamic changes of these measures in response to the low dose 1ug ACTH test.

Goals: To characterize the relationship between basal and dynamic cortisol response to an intravenous bolus dose of 1 ug ACTH in obesity.

Methods: Total, free and salivary cortisol were tested at the basal state and after a standard challenge with 1 ug ACTH in 22 healthy obese subjects (mean BMI= 42) and 17 healthy lean controls (mean BMI=22).

Results: Mean (+/-SD) basal state total cortisol was significantly lower in obese than in lean subjects (11.7+/-3.6 vs. 15.5+/- 4.4 ug/dl, p=0.006) as were also basal state serum free cortisol (0.53+/-0.24 vs 0.76+/-0.36 ug/dl, p=0.004) and basal statesalivary cortisol (0.23+/-0.10 vs. 0.56+/-0.66 ug/dl, p=0.004). Additionally, baseline total cortisol was inversely related to BMI (r= -0.45, p<0.05), to waist circumference (r= -0.49, p<0.05) and to systolic blood pressure (r= -0.39, p<0.05). Upon challenge with 1ug ACTH, total cortisol response as assessed by either repeated measure ANOVA (p=0.019) or area under the response curve ((P=0.028) was also lower in obese than in lean subjects. Concordant with these findings peak post-1ug ACTH salivary cortisol was lower in the obese relative to the lean subjects (1.14 +/- 0.10 vs. 1.65+/- 0.66 ug/dl, p<0.05)

Conclusion: Basal state as well as peak stimulated cortisol and integrated post-1ug ACTH-stimulated total serum cortisol levels, while within the test-defined normal range, were significantly lower in obese subjects. Obesity is not associated with higher basal cortisol or ACTH-stimulated cortisol reserve and indeed is linked to diminished circulating cortisol which is negatively related to body mass index and waist circumference. In fact, increased serum or salivary cortisol is atypical for obesity and should not be viewed as probable "pseudo-Cushing syndrome".

P-8

Autocrine function of adiponectin during differentiation: a healthy adipocyte is born (ID: 62)

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Background: Adiponectin is a known beneficial adipokine, improving insulin sensitivity and reducing inflammation. The aim of this study was to clarify the autocrine effects of adiponectin on adipocytes function.

Methods and results: 3T3-L1 preadipocytes were treated with Adiponectin from 2 days following confluency until the 12th day of differentiation. Rate of proliferation as measured by XTT reagent was increased by adiponectin. Adiponectin did not affect mRNA expression of adiponectin or AdipoR2, but increased that of AdipoR1. PPARgamma and perillipin mRNA expressions were lower in adiponectin-treated adipocytes. This was accompanied by a reduction in triglyceride accumulation as measured by Oil-red-O staining and TG assay kit. In order to clarify whether lipolysis or lipogenesis are regulated by adiponectin, glycerol release and mRNA expression of FAS, HSL and ATGL were measured. Although mRNA expression of HSL was not affected by adiponectin, basal lipolysis was increased. In addition, FAS expression was inhibited by adiponectin, indicating that adiponectin regulates both lipolysis and lipogenesis pathways. To investigate the effect of adiponectin on inflammatory response induced by lipopolysacharide (LPS), cells were treated with adiponectin during differentiation process ("chronic") or 24 hours before induction of inflammation in differentiated adipocytes ("late"). LPS induced inflammatory response, as indicated by 40 fold increase in IL6 mRNA expression. While "late" treatment reduced LPS-induced IL6 expression by 42%, "chronic" adiponectin completely blocked LPS-induced IL6 expression.

Conclusions: In conclusion, elevated adiponectin concentration at differentiation may lead to increased adipocyte number, with reduced lipid content and high resistance to inflammatory stimuli. The molecular mechanisms mediating these effects are currently being investigated.

P-9

Diabetic neuropathic cachexia: challenges and priorities of clinical practice: a case report (ID: 69)

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We report a case of diabetic neuropathic cachexia (DNC), complicated with a hyper functioning autonomous thyroid nodule, and undiagnosed Acromegaly.
This report illustrates a unique case where coexisting morbidities pose clinical management challenges, as to the proper priorities to be taken in the course of investigation and treatment.
It emphasizes a fast recovery from this remediable disorder, with anti neuropathic medications and insulin as an anabolic hormone.
It is recommended to consider DNC whenever an intense neuropathic pain dominates patient complaints, accompanied with anorexia, weight loss as well as mood and sleeping disturbances, whenever neoplastic disease prove not causative.
Raising DNC suspicion early and concomitant to weight loss investigation might lend shortening of suffering and an early recovery from a severe but otherwise has a good prognosis illness.
Shared findings of DNC, cancerous etiology and acute phase response are discussed.

P-10

The role of hypercholesterolemia on cancer risk and cancer-related mortality (ID: 72)

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Background: Hyperlipidemia and hypercholesterolemia have been found to be important factors in cancer development and metastasis. Moreover, statin therapy is deemed protective against cancer risk and cancer-related mortality. However, the metabolic mechanism and downstream cellular processes following cholesterol stimulation are still unknown.

Methods and results: Here we tested the effect of cholesterol on MC-38 colon cancer cells. Using Illumina gene array technology we found a number of genes that were differentially expressed following short term (20-40 minutes) and longer term (between 2-5 hours) cholesterol stimulation. Three genes were consistently increased at these time points, c-Jun, Jun-B and the chemokine CXCL-1. We have previously shown that cholesterol stimulation leads to PI3K/Akt phosphorylation, and now demonstrated that cholesterol inhibits ERK1/2 phosphorylation, both effects reversed when cholesterol is depleted from lipid rafts using methyl-b-cyclodextrin (MBCD). In addition, vanadate, an inhibitor of phosphatases, reversed the cholesterol inhibition of ERK1/2 phosphorylation. Specific inhibition of p-Akt by wortmannin did not affect cholesterol's stimulation of the expression of c-Jun and Jun-B, however the vanadate effect of increasing p-ERK1/2, inhibited c-Jun expression, specifically, and the MBCD effect of increasing p-Erk and inhibiting p-Akt reduced c-Jun expression. In contrast MBCD and vanadate both enhanced Jun-B gene expression in the presence of cholesterol and elevation of Erk phosphorylation.

Conclusions: These data point to a differential signaling pathway whereby cholesterol enhances gene expression of the Jun family members, and suggest possible future therapeutic targets for the hypercholesterolemic effect on cancer outcome.

P-11

Predictors of resting metabolic rate in healthy obese children aged 5-11 (ID: 76)

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Objective: To examine the role of a wide range of anthropometric, clinical, and biochemical parameters in the prediction of resting metabolic rate (RMR) in obese children. Research Methods The study included 60 healthy obese children who were tested for RMR at a tertiary pediatric medical center in 2004-2005 comprising 29 boys and 31 girls aged 5-11 years (mean 8.5±1.73 years), mean body mass index–standard deviation score (BMI-SDS) was 4.09±1.5. The following parameters were analyzed for each patient: anthropometric -- weight, height, mid-arm volume, waist girth, hip volume, waist–hip ratio, body surface area, free-fat mass, percent fat, clinical -- age, sex, ethnic origin, parental weight, birth weight, breastfeeding, hyperactivity, blood pressure, sexual development, biochemical -- blood count, lipid profile, inflammation markers, and levels of hunger and satiety hormones, thyroid hormones, glucose, and insulin. Computing-intensive applications software was used for multiple comparisons to identify significant predicting factors.

Results: Free fat mass was the best predictor of RMR (α=0.000, R^2=0.539), explaining 55% of the variance. The addition of BMI-SDS improved the model (α=0.000, R2=0.576). Presence of components of the metabolic syndrome and levels of hunger and satiety hormones as well as gender and maternal obesity did not have added value in explaining the variance. Leptin, Gerlin and HOMA are examples of 21 variables that had statistically significant correlations with measured RMR (0.273 α = 0.034, 0.87 α = 0.000, 0.326 α = 0.01 respectively). 11 variables (for example: Fleischer equation, BSA, the root of the circumference of the hip, root of the circumference of the arm, skin folds.) remained statistically significant even after applying the most stringent method dealing with multiple comparisons.

Conclusions: This study looked at a comprehensive list of anthropometric, clinical, and biochemical variables and their association with RMR. The results support earlier findings that free fat mass is the best predictor of RMR in obese children. Future studies should address the possible association between levels of hunger and satiety hormones and RMR.

P-12

Ethiopian Jews immigration to Israel in terms of diabetes mellitus outcomes (ID: 80)

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OBJECTIVE: The mass migration of Jewish Ethiopians to Israel began abruptly in 1984. Upon arrival in Israel, health status of the Ethiopians was characteristic of the country of origin: undernourishment was prevalent and type 2 diabetes (DM) occurred in <1% of immigrants. Within 10 years of residence in Israel and with exposure to urban-industrial lifestyles, the prevalence of DM in adults rose to 16%. The medical outcome of Ethiopian Jewish Israelis (EJI) who developed DM after migration to Israel is unknown. Our goal was to determine if the severity of diabetic complications differed in Israelis from Ethiopia vs industrialized countries.

RESEARCH DESIGN AND METHODS: From 2003 to 2012, a prospective study of 223 patients with DM (34% EJI, 44% male, age 62±13y, (mean±SD)) receiving health care at the largest HMO in Israel, was undertaken. Each EJI participant was matched to the two control non-EJI by age and sex.

RESULTS: Naturally, on 2003 compared to non- EJI, EJI had shorter citizenship period (15±3 vs. 40±13y, P<0.01). They had shorter duration of DM (5±4 vs. 10±8y, P<0.01), lower BMI (24.8±4.0 vs. 30.2± 5.0, P<0.05), lower rate of smoking (3% vs. 52%, P<0.01) and less volitional physical activity (15% vs. 42%, P<0.01). In addition, at baseline and at 10y, compared to non- EJI, the prevalence of hypertension, dyslipidemia, micro-vascular and macro-vascular complications of DM was lower. Moreover, even after adjustment for duration of DM, severity of DM and anti-diabetic drug treatment, death rate was lower in EJI than non- EJI (13% vs. 36%, P<0.01).

CONCLUSIONS: Even though diabetes occurs at a lower BMI in Ethiopians than other Israelis, diabetic complications and mortality are less severe. This could possibly be due to a lower rate of smoking, preimmigration life style and yet to be identified genetic factors.

P-13

Sexual dimorphism in the weight loss achieved in the treatment of the metabolic syndrome: women do better, again… (ID: 81)

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Background: Obesity, particularly abdominal obesity, is associated with insulin resistance leading to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Co-occurrence of metabolic risk factors for T2DM and CVD suggested the existence of a "metabolic syndrome" (MetS). The prevalence of MetS increases with age. Older age and obesity are two of the most powerful risk factors for uncontrolled hypertension, a major determinant of stroke and mortality, particularly in older age. Attempted weight loss is associated with lower all-cause mortality, regardless of age.

Aims: To compare the effects of 1year intensive nutritional control and tailored exercise program in younger and older MetS patients.

Methodology: Presented preliminary results are based on 31 patients that completed 1 year of intervention involving frequent interaction with a multidisciplinary team comprised of physicians, dietician and a physiologist. The range of patient ages was 21-74 with a median age of 55. Nine men were above and 9 below the median age, five women were above and 8 bellow median age. If needed, patients were medicated to control hypertension, dyslipidemia. In addition patients were offered weekly personalized dietary and physical exercise guidance. Upon recruitment and a year after body composition and body weight were measured

Results: Gender: In women baseline weight, total lean mass and total gynecoid and android fat mass, positively correlated with weight loss regardless of age ($r=0.8$, 0.56, 0.62 and 0.72, respectively, $p<0.05$). In contrast, in men there was a negative correlation between baseline weight, BMI, android fat and total lean tissue to weight loss, after 1 year of intervention ($r= -0.57$, -0.56 and -0.56, respectively, $p<0.05$). Gender and Age: Baseline lean mass was positively related to weight loss in younger women ($r= 0.72$, $p<0.05$) but correlated negatively with weight loss in men ($r= -0.71$, $p<0.05$). In older men gynecoid fat mass positively correlated with weight loss ($r=0.83$, $p<0.05$)/

Conclusions: In the context of MetS, women with higher baseline body mass (accounted for by higher lean and regional fat tissues) and older men, with feminine-like fat distribution, were the best weight losers

P-14

Pre-existing dysglycemia is a negative predictor of weight loss achieved in a multidisciplinary intervention program in non-diabetic women with the metabolic syndrome (ID: 83)

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Background: Lifestyle modification targeting physical exercise, better nutrition and weight loss and are the hallmark of current therapy of the metabolic syndrome, but treatment failure and progression to diabetes and/or other complications of the metabolic syndrome are rather common.

Aim: To evaluate how baseline features affect weight loss. Presented are the results of the first 33 subjects in an ongoing multidisciplinary interventional program in non-diabetic subjects with the metabolic syndrome.

Methods: Inclusion criteria were ages 18-75yrs and the ATPIII criteria to define the metabolic syndrome, with the exception of type 2 diabetes. Baseline assessment included standard clinical and biochemical profiling, exclusion of obesity secondary to endocrine derangement, nutritional questionnaire, 24 ambulatory blood pressure monitoring, subcutaneous periumbilical fat biopsy, body composition with DEXA, arterial properties (rigidity, compliance, pulse wave velocity) and muscle-strength. Intervention included frequent interactions with a multidisciplinary team including an endocrinologist and dietician with personalized physical training.

Outcome: This first cohort graduating from the program included 18 men and 15 women, with pre-intervention respective mean age of 52.2 and 54.8 years, weight 106.6 and 84.5, BMI of 34.3 and 32.2kg/m2. Mean attained loss was 7.9 kg in men (range: +6.3 to -23.6kg) and 8.7 kg in women (range: -4 to -24.6kg). Within this overall similarity in achieved weight loss, specific gender and age-related patterns emerged. A) Lean mass loss did not occur, on the average, in young men (<54yrs) (actual mean gain of 0.83kg) but was notable in older men (54yrs, -1.88kg) as well as in young and older women (2.47 and 1.57kg, respectively). B) In women, the presence of dysglycemia defined as either impaired fasting glucose or HgbA1C >5.7% but<6.5% was negatively associated with the achieved the percent weight loss 7.6 vs. 17% (p=0.012), fat mass loss 4.9% vs. 17.6% (p=0.07) and lean mass loss 1.9 vs. 10.4% (p=0.025) in dysglycemic and normoglycemic women, respectively.

Conclusion: In non-diabetic women with the metabolic syndrome, the presence of impaired fasting glucose or/and HgA1C in the "pre-diabetes" range is negatively related to the achieved weight loss in an intensive, multidisciplinary intervention program.

P-15

Hepatitis in an infant treated with octreotide for congenital hyperinsulinism (ID: 88)

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Preface: Congenital hyperinsulinism is characterized by hypoglycemia caused by several genetic disorders of inappropriate insulin secretion. Octreotide, an analogue of somatostatin, plays a major role in the pharmaceutical treatment of this condition

Patient: A 9-month-old infant treated with octreotide developed anicteric hepatitis with no other proven cause. After the discontinuation of this drug, the liver enzymes declined rapidly.

Conclusion: Liver function tests should be followed in patients receiving octreotide.

P-16

Estradiol-17β enhances pancreatic beta cell proliferation through different estrogen receptors in a glucose dependent manner (ID: 91)

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Background: Functional β-cell mass is reduced in both type1 and type2 diabetes and its protection is a long thought after therapeutic target. Estrogen deficiency, such as that occurring in menopause, predisposes to the metabolic syndrome and diabetes. The three estrogen receptors ERalpa, ERbeta and G-protein coupled ER (GPER) have been identified in rodent and human pancreatic β-cells. Estradiol-17β (E_2) has been shown to modulate insulin secretion and protect pancreatic β-cells against lipotoxicity, oxidative stress and apoptosis. Mechanisms implicated in E_2 protective effects include both the genomic and the extranuclear/membrane associated pathways occurring through rapid activation of ion channels and protein kinases.

Aim: We attempt to delineate the effects of E_2 as mediated by the different estrogen receptors on glucose stimulated insulin secretion (GSIS) and β-cell proliferation in states of normo- and hyperglycemia. We also speculate that E_2-induced β-cell proliferation may be mediated, in part, through the FOXO1 transcription factor.

Methods and Results: Effect of E_2 on insulin secretion was assessed by incubating the INS1 (rat insulinoma) cell line with E_2, the ERalpha agonist PPT, the ERbeta agonist DPN or the GPER agonist G1 each at 10nM, followed by GSIS. Insulin was quantified by RIA. One hour of treatment with E_2 and agonists significantly augmented insulin secretion at 2.8mM but not 16.7mM glucose. Effect of E_2 on proliferation was assessed by thymidine incorporation. Cells were grown under conditions of normoglycemia, short hyperglycemia (28mM glucose for 24h) or prolonged hyperglycemia (28mM glucose for 5 days) and treated with E_2 and agonists 10nM each for 24h. Cells under normoglycemia doubled proliferation with all treatments. Cells under short hyperglycemia doubled proliferation only when stimulated with PPT. Cells exposed to prolonged hyperglycemia increased proliferation by 9 times when treated with E_2 but only doubled proliferation with the different agonists. Cytoplasmic FOXO1, as assessed by western blot analysis, was reduced 30 min after exposure to E_2.

Conclusions: Our results suggest that E_2 induced β-cell proliferation is mediated by different ERs depending on conditions of exposure to hyperglycemia. We also suggest that FOXO1 may be involved in E_2 proliferative effects.

P-17

Gender and age, but not obesity, affects serum dexamethasone and/or cortisol levels post overnight 1 mg dexamethasone suppression test (ID: 93)

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Background: Cushing's syndrome (CS) is often considered, though rarely encountered in the work-up of obesity. The overnight 1 mg dexamethasone suppression test (ODST) is widely used in this setting. Confusingly, obese subjects were shown to be either Dex hypersensitive (better suppressors) or require higher Dex dose to achieve proper suppression. The latter is due to a higher volume of distribution that consequently lowers the achieved serum Dex, with inadequate Hypothalamus-Pituitary-Adrenal axis suppression. Here we re-assessed this debatable issue.

Aim: To evaluate the outcome of ODST in obese versus non-obese subjects, not suspected as having CS.

Methods: Blood samples for baseline cortisol (at 8:00 AM) were obtained from 59 volunteers whose BMI ranged from 17.9 to 47.5 kg/m2. The morning (8:00-9:00 AM) following ODST (at 11:00 PM) blood samples for serum cortisol and Dex levels were collected and determined by ELCIA [Cobas 411) (cortisol) and HPLC (cortisol, Dex). Results: All but one of the participants properly suppressed serum cortisol level to <1.8 µg/dL, All but 5 suppressed to<1.4 µg/dL. Men with BMI≤30 had a significantly higher serum Dex level than women with a similar BMI (0.67±0.38 vs. 0.36±0.19 ug/dL, p=0.01). The difference in Dex levels did not translate, however, into gender-related differences in attained cortisol. While there was no correlation between Dex and post-Dex cortisol, serum Dex in the 5 individuals who failed to show suppression was ≤l ug/dL. Post Dex serum cortisol correlated positively with age (r=0.45 by RIA, r=0.27 by HPLC, adjusted for BMI, p<0.05 for both tests), but not with BMI. Subdivided by body mass, subjects with BMI≥25 vs. those with BMI<25, had substantially higher HPLC- (but not ELCIA) determined cortisol levels (1.16±0.57 vs. 0.86±0.33 µg/dL, p=0.044).

Conclusions: Age, but not elevated BMI, is linked to lesser suppression of cortisol by Dex. Therefore, ODST is equally reliable in normal weight, overweight and obese subjects, with no need for Dex dose adjustment. Because of some disparity between HPLC and RIA-determined cortisol levels in the low concentration range seen with suppression, borderline and unexpected results should be clarified by the measurement of cortisol and Dex by HPLC.

P-18

GTF - an anti diabetic material extracted from yeast decreases high glucose damages in endothelial cells (ID: 103)

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Background: Among the severe complications of diabetes are macro and micro vascular diseases, leading to CVD, strokes, nephropathy, and retinopathy. Endothelial dysfunction is the initiating event in the process of atherosclerotic plaque formation, comprising of impaired vasodilatation, inflammatory process, increased arterial stiffness and reduced NO production. Oxidative stress plays a key role in the pathogenesis of vascular complications. Addition of insulin to endothelial cultures protects the cells from damages caused by high glucose and oxidative stress.

Aim: The aim of our study was to investigate the mechanism involved in high glucose damage to endothelial cells in vitro, and to examine the effects of Glucose Tolerance Factor (GTF), an anti diabetic agent extracted from yeast, on these parameters in endothelial cells. Previous studies done in our laboratory showed that oral treatment with GTF decreased blood glucose and lipids and potentiated insulin action in both types of diabetes. In vitro studies in adipocytes and myocytes showed that GTF phoshorylated key proteins along insulin signaling pathway.

Results: In the present study we found that high glucose decreased ABAE endothelial cells proliferation to 83.9% and 60.2% of normal rate (for x5 and x10 glucose, respectively). Addition of GTF (5mg/ml) increased the proliferation to 98.9%, and 75.4% (for x5 and x10 glucose, respectively). High glucose impaired anti oxidative enzymes activity: x10 glucose decreased catalase activity to 83.7% and SOD activity to 72.3% compared to normal glucose conditions. Addition of GTF (1mg/ml) to high glucose (x10) conditions, increased catalase and SOD activities to 100.5% and 92% respectively. High glucose x10 impaired NO production in endothelial cells to 70.7% of normal conditions. Addition of GTF (1mg/ml or 5mg/ml) to high glucose conditions reversed NO production to 84.1% or 89.2% respectively. Treatment of ABAE cells with GTF increased the phosphorylation of key proteins (AKT, MAPK. PTEN, eNOS) along insulin signaling pathway. GTF activity was dose and time dependent and was found for both normal and high glucose conditions.

In summary: our findings present GTF as a novel insulin-like material which can protect endothelial cells from high glucose damage.

P-19

High prevalence of obesity in children in northern Israel (ID: 107)

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Background: Childhood and adolescent obesity is an emerging problem in the western world and increased dramatically during the last four decades. Limited data is available on the prevalence in Israel.

Objective: To determine the prevalence of childhood and adolescent obesity in Northern Israel and to evaluate the availability of fast food and food with a low nutritional value in Afula city.

Methods: We conducted a review of the electronic medical records of the Clalit Health Services, recording body mass index (BMI), age, gender and residence in two separate periods, between the years 2010-2012 and 2006-2007. BMI was calculated as SDS for age and gender according to the CDC charts. Overweight was defined as BMI above 85th centile and obesity as BMI above 95th centile. 94,239 subjects were enrolled between the ages 2-18 years. Mapping of the availability of fast food and fresh food was performed in Afula city.

Results: Twenty four percent of the children had BMI above the 85th centie (10.5% were obese). The prevalence of obesity was higher in males (11.5% vs. 9.5%, $p<0.0001$). Both overweight and obesity peaked in girls at the age 9 and in boys at 11 years (33%, 30.5, respectively). Jews were more overweight then Arabs. The prevalence of overweight and obesity was higher in the urban regions when compared with the rural regions. No increase in the prevalence of obesity was observed between the years 2006-2007 and 2010-2012. Field mapping of Afula demonstrated a paucity of fresh fruit and vegetables when compared with the abundance of nutrition-poor food. 72% of 193 stores sold nutrition poor foods and only 7.5% sold fruits and vegetables. In summary, a high prevalence of overweight and obesity was found in Northern Israel. The fact that there was no increase in the prevalence of obesity during the last 5 years may suggest that obesity has approached its peak.

Conclusions: It is necessary to plan a national intervention for the prevention of obesity among children. More studies should be conducted to explore the association between the intake of poor nutritional food and obesity among children in Israel.

P-21

The efficiency of intraosseous human growth hormone administration: a feasibility pilot study in a rabbit model (ID: 7)

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Background: The use of protein- and peptide-based drugs in the treatment of disease has significantly increased in recent years. However, their chemical and physical properties make them unsuitable for simple oral delivery.

Aim: The objective of this proof-of-concept study was to examine the feasibility of protein administered via intraosseous (IO) injection. Human growth hormone (GH), a 22KDa protein, served as the model protein.

Results: An indwelling IO needle and intravenous (IV) line were placed in four rabbits, and 50mcg/kg, 100mcg/kg, 200mcg/kg, or 400mcg/kg of GH were injected. Blood samples were taken at different time points and analyzed for GH concentration. There were no significant pharmacokinetic differences between the IO and IV routes. For the 400mcg/kg dose, the area under the serum GH concentration time curve (AUC) was 100.55±46.7mcg/min*ml with IV administration and 84.6±34 mcg/min*ml for IO (p=0. 73 compared to the IV route), C_{max} measured 11.2±5mcg/L and T_{max}, 0.9±0.7min. For the 200mcg/kg dose, the AUC was 68.5±16.7mcg/min*ml with IV administration, and 85.1±1.5mcg/min*ml (p=0.39) for IO, C_{max} measured 8.13±2.44mcg/L and T_{max}, 1.92±1.06min.

Conclusions: The present study is important because it shows bioequivalence of a protein, GH, delivered via the IO or IV route, with no significant differences in rate or extent of drug exposure, half-life, clearance, or volume of distribution. Our findings suggest that the physicochemical properties of GH (22KDa) do not affect its pharmacokinetics (mainly absorption) and thereby, its bioavailability in the central circulation. IO protein injection is associated with greater ease, control, and predictability than SC injection. Thus, the present study may open the way for the use of IO delivery as an alternative route of protein delivery. Further studies with a larger number of animals are required to evaluate the pharmacokinetics and pharmacodynamics of high-molecular-weight proteins injected by the IO route.

P-22

HDAC10 is involved in food restriction-induced growth arrest (ID: 9)

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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. We decided to check the involvement of HDACs as they were shown to alter global gene expression.

Methodology: 1. Prepubertal rats were subjected to 10 days of 40% food restriction, followed by a renewal of unlimited food supply for one day. 2. Molecular analysis was performed in in vitro model consisting of hepatocyte cell lines.

Results: Food restricted rats had a significant lower weight, which was immediately increased already after one day of re-feeding (by 18%, $P<0.001$). Similar changes were observed also in the weight of several internal organs (kidney, lungs, liver and heart) with the most dramatic effect noted in the liver (186% increase after one day of re-feeding, $P<0.01$). Interestingly, the protein levels of HDAC10 in the liver were significantly increased by food restriction and immediately reverted to normal levels after one day of re-feeding, no changes were noted in the mRNA levels. Similar increase was noted after 48hrs of serum starvation of Huh7 hepatocyte cells. Inhibition of mTOR activity by rapamycin in these cells led to a similar increase in HDAC10 suggesting that mTOR may mediate the effect of nutrition on HDAC10.

Conclusion: This is the first time that the role of HDAC10 in normal tissues is being explored. Our results suggest that the epigenetic effect of nutrition on growth may be mediated by HDAC10, as HDAC10 is sensitive to the nutritional status, through mTOR. Studying the role of HDAC10 in growth regulation process may help design new therapeutic strategies.

P-23

Identification and characterization of a novel insulin-like growth factor 1 receptor gene heterozygous mutation in a child with growth failure (ID: 18)

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Background: Insulin like growth factor 1 receptor (IGF1R) is a tetrameric (α2β2) cell-surface tyrosine kinase receptor that mediates the mitogenic effects of IGF1. Heterozygous mutations in the IGF1R gene lead to intrauterine growth retardation (IUGR) with postnatal growth failure. We identified a novel heterozygous IGF1R mutation, G to A nucleotide exchange 1bp after exon 1 ORF (c.94+1g>a/N) in a 3 years old boy (index case) and his mother. The child presented with IUGR, recurrent hypoglycemic episodes and postnatal growth failure. The aim of the present study was to characterize and investigate the function of the IGF1R via the heterozygous mutation identified.

Materials and methods: Fibroblast cultures of index case and mother were initiated from skin biopsies. For control purposes, fibroblasts of age- and sex-matched donors were used. IGF1R and InsR protein expression and the downstream signaling proteins, Akt and ERK, were measured by Western blotting using specific antibodies. Real-time PCR was performed to assess IGF1R mRNA content in the patients and controls.

Preliminary Results: Treatment with low doses of IGF1 led to increased IGF1R phosphorylation in mutant fibroblast from the child as compared to control and to mutant fibroblasts from his mother. However, after treatment with normal or high doses of IGF1, decreased IGF1R phosphorylation was observed in mutant fibroblasts from the child and his mother compared to control. In addition, IGF1R mRNA levels were lower in our index case compared to another heterozygous IGF1R mutation case but higher compared to his mother.

Conclusions: We diagnosed a child with a novel mutation of the IGF1R gene. The results so far may suggest that there is a compensatory mechanism which involves up regulation of the WT IGF1R or a higher sensitivity of the receptor in the child. Further studies are required to understand the biological and genomic significance of the mutation.

P-24

Valporic acid in combination with chemoradiotherapy using gemcitabine for enhanced treatment of pancreatic cancer (ID: 22)

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Introduction: Pancreatic cancer (PaCa) is the 4th most common cause of death from malignancy. A considerable number of PaCa patients first present with locally advanced unresectable disease. For these patients, concurrent chemoradiotherapy (CCRT) using gemcitabine (Gem) is a standard treatment. However, results remain dismal. The aim of the present study was to design an effective treatment for unresectable locally advanced PaCa. The recurring evidence that valproic acid (VPA) effectively sensitizes cancer cells to DNA-damaging agents due to its histone deacetylase - inhibiting activity prompted us to inquire whether combination of VPA with Gem-based CCRT would ultimately enhance the response of PaCa to Gem-based CCRT treatment. This hypothesis was tested in an in vitro system.

Methods: PaCa cell line Panc-1 was treated for 48 h with 10 nM Gem or 2 mM VPA, or their combination followed by ionizing radiation (IR) with a dose of 2 Gy. Cells were incubated for additional 120 h. The effects of treatments on cell proliferation, cell-cycle and apoptosis were evaluated.

Results: Treatment of Panc-1 cells with 10 nM Gem, 2 mM VPA or 2 Gy IR alone decreased cell growth by 37.0%, 34.0% and 15.1%, respectively. Combination of Gem and VPA was more effective and decreased proliferation by 54.6%. Combination of IR with either Gem or VPA suppressed cancer cell proliferation by 46.0%. However, triple combination of agents was mostly efficient and decreased proliferation by 67.9%. The cell growth-inhibiting effect of treatments was a result of both cell-cycle arrest in S-phase and enhanced apoptosis. The pro-apoptotic effect was particularly pronounced in cells treated with the combination of Gem and VPA, and in cells challenged with the combination of 3 agents.

Conclusions: The results are consistent with our hypothesis that co-administration of VPA may enhance the anticancer activity of Gem-based CCRT in Pancreatic Cancer.

P-25

The effect of leptin administration on mammary tumor growth in diabetic mice (ID: 26)

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Background: Obesity, the metabolic syndrome and type 2 diabetes are associated with an increase in many various cancers. Obesity is associated with hyperleptinemia and this has led to the suggestion that leptin may be a factor in cancer progression. Leptin stimulates cancer cell growth in culture, but leptin administration in vivo has not yet been studied to determine its effect on tumor progression.

Results: When administered to the MKR mice, both male and females, that represent a model of non-obese type 2 diabetes, leptin failed to stimulate tumor progression, indeed, in the studies where glucose tolerance improved tumor growth was actually inhibited.

Conclusions: Thus while endogenous hyperleptinemia maybe a factor in cancer growth and outcomes in obesity and prediabetes, exogenous leptin does not promote tumor progression. The possibility exists that the effect of leptin on tumor progression maybe opposed by improvements in metabolism, and further studies are needed to establish this possibility.

P-26

Regulation of IGF1R gene expression and action by the androgen-regulated fusion protein TMPRSS2-ERG in prostate cancer (ID: 33)

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Background: Prostate cancer is the second most frequently diagnosed malignancy and one of the leading causes of cancer related death in men. The IGF1R axis plays a key role in prostate cancer initiation and progression. Recently, the group of A. M. Chinnaiyan identified recurrent gene fusions of the 5' untranslated region of the TMPRSS2 gene to members of the ETS transcription factor family in prostate cancer. As a result of the inclusion of the androgen sensitive TMPRSS2 promoter, cells expressing the fusion protein exhibit an androgen-regulated expression of ERG. Consequently, ERG was identified as the most commonly overexpressed oncogene in prostate cancer. The aim of the present study was to analyze the involvement of the prostate cancer-specific TMPRSS2-ERG fusion protein in the regulation of IGF1R gene expression and to investigate the regulation of the IGF1 signaling pathway by TMPRSS2-ERG.

Materials and methods: M12, a metastatic prostate cancer cell line, was infected with a T-ERG expression vector. VCaP, a TMPRSS2-ERG (T-ERG)-expressing bone metastasis-derived cell line, was transfected with a siRNA directed against the fusion protein. Protein levels of IGF1R and ligand-induced phosphorylation of IGF1R and downstream signaling proteins, Akt and ERK, were measured by Western blotting using specific antibodies. Transient co-transfections were performed in the M12 cell line using the chimera-encoding expression vector, along with an IGF1R promoter luciferase reporter plasmid. Forty eight hours post transfection cells were harvested and luciferase activity was measured.

Results: M12 stable transfectants showed elevated levels of IGF1R protein as compared to control, untransfected cells. In VCaP cells, the decreased protein level of T-ERG as a result of the siRNA treatment was associated with reduced IGF-IR protein level as compared to control. In addition, IGF1R promoter activity in T-ERG-expressing M12 cells was higher than in control M12 cells.

Conclusions: Our preliminary data indicate that T-ERG positively regulates IGF1R gene expression, hence providing support to the notion that the IGF1R gene constitutes a novel downstream target for TMPRSS2-ERG action. Identification of the mechanisms of action of TMPRSS2-ERG in prostate cancer may have important basic and clinical relevance.

P-27

Identification of tumor protecting pathways in Laron Syndrome patients (ID: 36)

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Background: Laron syndrome (LS) is a human genetic disease that is caused by molecular defects (deletion or mutation) 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. The IGF system has a key role in mediating GH-induced growth, differentiation and developmental processes. Overexpression of IGF1 or its receptor is a typical hallmark of most pediatric and adult tumors. Consistent with the prosurvival, antiapoptotic role of IGF1, recent epidemiologic studies reported that patients with congenital IGF1 deficiency, including LS, 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.

Methods: Epstein-Bar virus (EBV)-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. Proliferative and antiapoptotic effects of IGF1 were determined by XTT assays. Genome-wide gene expression analyses were conducted using RNA obtained from patients and controls.

Results: Western blot analysis revealed that LS-derived lymphoblastoids express higher levels of a number of tumor suppressors, including pTEN, p21 and p53, than relatives. On the other hand, levels of positive regulatory proteins, including transcription factor Sp1 and cyclin D1 were lower in LS patients. In addition, XTT assays revealed a reduced proliferative response in LS cells.

Conclusions: Our preliminary analyses provide evidence that proteins associated with tumor suppressing, pro-apoptotic pathways are overrepresentated in LS patients whereas proteins involved in proliferative events are underrepresented. These results may generate relevant information regarding preferential activation of protective signaling pathways in LS patients. The specific mechanisms responsible for cancer protection in LS patients remain to be established.

P-28

Identification of BRCA1 as a biomarker for IGF-IR targeted therapy in breast cancer (ID: 39)

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Background: The insulin-like growth factors, IGF-I and IGF-II, are a family of mitogenic polypeptides with important roles in growth and differentiation. The biological actions of the IGFs are mediated by the IGF-I receptor (IGF-IR). The IGF-IR plays a key role in tumor initiation and progression and it emerged in recent years as a promising therapeutic target in a number of malignancies. BRCA1 is a tumor suppressor gene which participates in multiple biological pathways. Our lab has previously shown that BRCA1 expression in breast cancer cells resulted in reductions in endogenous IGF-IR levels and IGF-IR promoter activity, suggesting that the IGF-IR gene is a downstream target for BRCA1 action. The main aim of this study is to evaluate the hypothesis that the efficacy of IGF-IR-directed therapies in breast cancer is heavily dependent on the BRCA1 status of the patient. Specifically, we postulate that the mutational and activation status of BRCA1 in breast tumors should predict responsiveness to IGF-IR inhibitors and, in particular, MK-0646, a selective IGF-IR monoclonal antibody.

Methods: To evaluate our hypothesis, the BRCA1-null HCC1937 breast cancer cell line was transiently transfected with a wild-type BRCA1-encoding expression vector. In addition, MCF10A and MCF7 cell lines were infected using the lentivirus vector pGIPZ encoding a BRCA1 shRNA. The cells were treated with MK-0646 antibody, after which cell proliferation, apoptosis, cell cycle progression and in vitro invasion and migration assays were performed.

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, these experiments will provide, for the first time, a correlation between BRCA1 status and the capacity of MK-0646 to target the IGF-IR in breast cancer.

P-29

Growth patterns in congenital multiple pituitary hormone deficiencies (Mphd) compared to that of Mphd following abnormal delivery (ID: 49)

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Background: Most publications do not distinguish between the different etiologies of perinatal MPHD.

Aim: To compare the perinatal and post-natal growth pattern in 2 groups of patients with MPHD including GH.

Subjects: Forty five patients (27m, 18 f): (37 Jews, 2 Muslims, 6 Christians) were diagnosed, treated and/or followed in our clinic until late adult age. 20 patients were of consanguineous families. Many were new immigrants. According to etiology they were divided into 2 groups: Gr I congenital MPHD (15m, 17f) and Gr II MPHD due to abnormal delivery (12m, 1f).

Results: Thyroid hormone was started in infancy in 27 patients. Age at referral of Gr II patients was younger than that of Gr I with abnormal delivery drawing earlier attention. 9 patients started hGH below age 6, and 6 below age 10. The main results are summarized in the Table.

Group	Sex n	At birth		Start of hGH		GH+sex hormones Rx		Final Ht. (cm)	Final HC (cm)	Present Age yrs
		Wt (kg)	Lgth (cm)	HC (cm)	Ht. (cm)	yrs	GV (cm/y)			
I	m 15	3.4 ±0.6	49 ±2.7	49.9 ±46	103.3 ±27.7	10.8 ±5.7	5.98 ±1.2	159.0 ±14	55.49 ±2.3	49.4 ±20.9
n=32	f 17	3.0 ±5.15	47.6 ±0.6	50.4 ±1.6	113.5 ±19.3	6.8 ±2.9	5.3 ±1.6	150 ±9.6	54.2 ±2	51 ±13.2
II	m 12	2.63 ±0.6	47.5 ±3.8	51.9 ±1.7	119.7 ±19	8.6 ±3.7	5.1 ±1.7	163.6 ±5.6	54.9 ±1.1	43 ±11
n=13	f 1	2.1		48	116	5	4.5	138.6	49	25.5

Results are mean±SD, HC=head circumference, Ht= height, GV=growth velocity.

Conclusions: The mean birth weight of the males in Gr I was higher than that in Gr II ($p<0.009$). The mean birth length of all neonates was greater than that reported for neonates with cong IGHD or cong IGFI def. but lower than that of healthy newborns. Final height of Gr I was slightly below the 3rd centile in both genders and slightly above that centile in males of Gr II. Education of the public improved referral and earlier treatment in last decades.

P-30

Non-functional pancreatic neuroendocrine tumors with transformation to insulinoma: an esoteric presentation of a rare disease (ID: 74)

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Most of the pancreatic neuroendocrine tumors (PNETs) are usually non-functioning, whereas insulinoma is the most common among the functioning tumors. Rarely, a nonfunctioning tumor can undergo biological transformation to a hormone secreting tumor with subsequent changes in the clinical presentation.
We present here two unique patients with longstanding PNETs who developed severe hypoglycemia with hyperinsulinemia, in parallel with tumor progression.
A 45 year-old women presented with abdominal pain, diarrhea and weight loss. Subsequent investigation revealed a pancreatic mass with secondary hepatic lesions, and a well differentiated grade 2 NET (KI-67 proliferation index- 5-7%) was diagnosed on pathology. A Gallium^{68} DOTATATE PET-CT showed high uptake by the pancreatic and hepatic masses. The patient was treated with somatulin and radio-labeled somatostatin analogues (PRRT) with disease stabilization. Several months later, the patient presented with severe episodes of hypoglycemia, together with high levels of serum insulin and C-peptide. A second biopsy revealed a higher proliferation index of 20%. Subsequent treatment with everolimus followed by streptozocin, DDP and 5-FU, resulted in resolution of the hypoglycemia and marked regression of the hepatic lesions. However, despite further PRRT, the patient died due to progressive disease one year later.
The second case is a 63 years-old man, diagnosed with a PNET following a work-up of chronic diarrhea. A 1.5 cm pancreatic mass with secondary hepatic lesions and celiac root lymphadenopathy was noted on initial CT examination. Biopsy showed a well differentiated NET grade 2. The patient was treated also with Somatuline Autogel and PRRT over a period of eight years. Recently, the disease progressed as reflected by clinical deterioration and Gallium^{68} DOTANOC PET_CT imaging. In parallel, the patient developed recurrent episodes of severe hypoglycemia in association with increased serum levels of insulin and C peptide. The patient was started on everolimus.
These two cases highlight the exceptional ability of PNETs to change their biological behavior in parallel with disease progression. Importantly, recent studies have demonstrated the efficacy of everolimus (Afinitor) in the control of both hypoglycemia and tumor progression.

P-31

Carotenoids and their derivatives inhibit IGF-I activity in breast cancer cells but enhance it in bone cells. (ID: 102)

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Background: Insulin-like growth factors (IGFs) are involved in tumor formation and progression. Blood IGF-I levels years before malignancy diagnosis correlate positively with the risk for breast and prostate cancer. In contrast, IGF-I is an important positive regulator of bone homeostasis throughout life. We have found that dietary carotenoids and polyphenols inhibit IGF-I-stimulated proliferation and AKT phosphorylation in breast cancer cells but do not inhibit and even enhance it in osteoblast cells.

Aims: The aim of the current study was to provide mechanistic explanation for the opposite effects of the dietary compounds in these two cellular systems.

Results: Since IGF binding proteins (IGFBPs) are known to regulate the biological activity of IGFs, we determined if dietary carotenoids and polyphenols affect IGFBP expression in cancer and bone cells. We first checked the level of IGFBP-3, the most abundant IGFBP in the blood, and found that it is expressed in human osteoblast-like cells (MG-63) but not in breast cancer cells (T47D and MCF-7). Treatment of MG-63 cells with IGF-I increased IGFBP-3 secretion into the medium whereas several dietary compounds - lycopene, lutein, carnosic acid and curcumin reduced secretion of this BP. This decreased BP-3 secretion was opposite to the increase in AKT phosphorylation caused by these compounds but the contribution of BP-3 to this effect is not clear yet. The tested dietary compounds are known to increase the level of Nrf2 which activate the antioxidant response element transcription system. Thus we determined if Nrf2 modifies the IGF-I response. We found that Nrf2 over-expression reduced the phosphorylation of AKT in cancer cells in a dose dependent manner, but increased it in bone cells.

Conclusions: In conclusion, we suggest that dietary carotenoids and polyphenols activate the Nrf2 transcription system in both cancer and bone cells. However, Nrf2 affect IGF-I signaling in these cells in opposing directions, stimulation in bone cells which can improve bone health and inhibition in cancer cells and thus contributing to cancer prevention.

P-72

Insulin/IGF-1-induced epigenetic changes in the brain (ID: 46)

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Background: In the USA, approximately 13% of people aged 65 and older, and more than 45% of people older than 85 have Alzheimer disease (AD). Meanwhile 42% of the population over 65 is afflicted with Diabetes Mellitus (DM). One of the characteristic features of AD is amyloidogenesis, i.e amyloid β (Aβ) formation in various brain regions. In addition hIAPP (human amylin) accumulates as amyloid fibrils on β-cells and is a typical hallmark of DM. Aβ and hIAPP can both aggregate to form extracellular plaques in brain and pancreatic β-cells, respectively.
Human Ca^{+2} binding protein nucleobindin 1 (NUCB1) has been identified as inhibitor of hIAPP fibrils formation and is also responsible for disaggregation of those fibrils. Neprilysin, on the other hand, is considered the rate limiting regulator of Aβ degradation. Neprilysin-deficient KO mice showed both an Alzheimer's-like behavior and Aβ deposition in the brain.

Our hypothesis is that long-term exposure to high levels of glucose and/or hyperinsulinemia may lead to epigenetic alterations in the brain, with ensuing changes in expression of genes associated with the etiology of neurodegenerative diseases, including AD. The aim of this study was to examine the potential epigenetic mechanism responsible for regulation of neprilysin and NUCB1 genes in brains of MKR mice, a validated model of hyperinsulinemia.

Methods: Brain, liver, pancreas and adipose tissue were obtained from 10-week old, male MKR mice (hyperinsulinemic / hyperglycemic). Glucose and insulin levels in serum were measured weekly. DNA and RNA were prepared. To assess DNA methylation, DNA was treated with sodium bisulfite. Specific mRNA expression will be assessed by qPCR.

Results: Preliminary analyses showed changes in the expression of genes related to neurodegeneration, including among others, APP, apoE, LDLR1 and MAT1A, between MKR and FVBN (control) mice. In addition decreases in Neprilysin and NUCB1 mRNA levels were observed in the brains and pancreata of MKR compared to FVBN mice.

Conclusions: Preliminary analyses suggest that certain epigenetic changes, secondary to DM, may affect the expression of proteins related to neurodegeneration. Furthermore, these findings may explain the association of DM with neurodegenerative disorders.

P-73

Clinical course and outcome of non-functioning pituitary adenomas in the elderly compared with younger age groups (ID: 54)

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Background: Non-functioning pituitary adenomas (NFPA) account for a third of pituitary tumors, and are the most common type diagnosed in older patients. However, there is insufficient data regarding the clinical course, risk of regrowth following surgery and long term prognosis in elderly patients compared to younger age groups.

Material and methods: A retrospective chart review identified 105 adult patients treated for NFPA between 1995 and March 2012, who were stratified into 3 age groups: 18-44 (29 patients), 45-64 (38 patients), and over 65 years old (38 patients). The impact of age on presenting symptoms, disease course and outcome was analyzed.

Results: Adenoma size was larger in patients younger than 45 years (mean 2.9 cm) compared to the other age groups (2.3 and 2.5 cm, p=0.05), with trans-sphenoidal surgery being the treatment of choice in all three groups (83%, 92%, and 84%, ns). After a mean follow-up of 6 years there were higher recovery rates from hypopituitarism in patients younger than 45 years (58% versus 27% and 24%, p=0.04). Visual field improved in most patients following surgery (74%, 94% and 86%), with a trend toward more full normalization in the young age group (58% versus 44% and 41%, p=0.09). There were no significant differences in the risk of remnant growth (29%-39%), rates of radiation therapy, or need for repeated surgeries. There were no disease related mortalities during the study period.

Conclusion: Elderly patients with NFPA have lower rates of recovery from hypopituitarism after treatment compared to younger age groups, with similar rates of regrowth and need for salvage surgery.

P-74

Non-functioning pancreatic neuroendocrine tumors (PNET): association with prediabetes/diabetes (ID: 56)

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Background: Neuroendocrine tumors of pancreas (PNET) are classified as functional or nonfunctional (NF) based on presence or absence of a clinical syndrome associated with hormone over secretion. NF-PNETs do however often produce low levels of- or inactive hormones (pancreatic polypeptide, calcitonin or neurotensin) which do not cause any symptoms.

Goals: This retrospective study was performed to evaluate if there is a metabolic impairment in NF-PNET.

Results: Thirty nine consecutive patients with histologically confirmed NF-NETs were assessed, with a F/M ratio 14/25, mean (+/-SD) age of 60.7±12.8 y, 22 with previous pancreatic surgery and 17 prior to/without surgery. Mean tumor size was 2.8±2.3 cm. More than two thirds (66%) of this cohort had impaired glucose metabolism: 44% (17/39) had overt diabetes mellitus (DM) and 23% had impaired fasting glucose (IFG). Mean (on treatment, in several patients) fasting glucose level was 111±21mg/dl, HBA1c 6.9±2.1% and BMI 28.7± 6.3 kg/m2. The rate of DM in subjects operated for PNET and subjects who were not operated on was 45% and 35%, respectively and the corresponding rates for IFG was 24% and 23%, respectively. BMI was lower in the subgroup subjected to surgery (26.1±2.4 vs. 32 ±8 kg/m2, $p<0.02$).

Conclusion: This is the first report presenting the surprising finding of a high prevalence of impairment in glucose metabolism in patients with NF-PNET. The high prevalence of diabetes/prediabetes cannot be attributed to age, obesity or surgery alone, though each could have a contributory role. If verified in larger series of patients, this observation should prompt re-examination of the term "non-functioning" in the context of PNET and/or raise the possibility of increased rate of "NF"-PNETs in type 2 diabetes/prediabetes.

P-75

KISS1 receptor is preferentially expressed in clinically non-functioning pituitary tumors and does not correlate with tumor size or invasiveness (ID: 57)

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Background: In addition to their involvement in cancer biology, the KISS1/KISS1R genes play a central role in the neuroendocrine regulation of reproduction. Given the high expression levels of KISS1 and KISS1R in the hypothalamus and the pituitary respectively, we hypothesize that this system could possibly affect the degree of tumor invasiveness and clinical behavior of pituitary tumors.

Methods: RNA was extracted from pituitary tumor samples obtained during transsphenoidal surgery. Expression levels of KISS1 and KISSR mRNA was evaluated by RT-PCR. Clinical information pertaining tumor characteristics was extracted from patients' charts.

Results: The study sample comprised of tumors from 41 patients (22 female, mean age 47.5 years). There were 19 nonfunctioning pituitary adenomas (NFPAs), twelve GH-, six ACTH-, and four PRL-secreting adenomas. KISS1 expression was undetectable in all pituitary tumor samples and in normal pituitary. KISS1R was expressed in 26 (67%) out of 39 analyzed samples (94% of NFPA, 42% of GH-, 67% of ACTH-, and 25% of PRL-secreting adenomas) and was found more often in female patients (81% vs. 50%), $p<0.05$, and in NFPA (94% vs. 45.5% in secreting tumors, $p=0.003$). Patients expressing KISS1R were older (50.5 ± 1.4 vs. 38.1 ± 1.3 years at presentation, $p=0.008$). There were no significant differences in KISS1R expression according to invasiveness or tumor grade. In the multivariate analysis, factors significantly associated with KISS1R expression included female gender (OR = 13.8, 95% CI 1.22-155.9, $p=0.03$) and having a NFPA (OR = 24.7, 95% CI 1.50-406.4, $p=0.02$). Tumor size, invasiveness and age at presentation were not independently associated with KISS1R expression.

Conclusions: We have demonstrated that the majority of human NFPA express KISS1R with lower rates of expression in other types of pituitary tumors, and that this expression was more often found in tumors excised from female subjects and at a higher age of clinical presentation. KISS1R expression did not impart a clinical beneficial tumor phenotype, as it was not associated with tumor size or invasiveness. Additional studies are required to elucidate the role of KISS1 and its receptor in pituitary gland physiology and pathology.

P-76

Male prolactinomas presented with normal testosterone levels (ID: 58)

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Background: In men harboring prolactinoma the most common symptoms are related to hypogonadism, including decreased libido, erectile dysfunction, and gynecomastia. These men characteristically present with elevated serum prolactin (PRL) levels, suppressed gonadotropins, and low testosterone levels.

Objective and Patients: Our study population includes 56 men with prolactinomas. The study compares a series of 11 unique men with prolactinomas presented with testosterone levels within the normal range (>2.6 ng/ml, Cohort A), and 11 men with borderline baseline testosterone (2.1-2.5 ng/ml, Cohort B) to the more common 34 prolactinoma patients presented with low testosterone levels (<2 ng/ml, cohort C).

Results: Mean testosterone levels at presentation were 3.91 ± 0.9 ng/ml in cohort A (range, 2.6-5.2 ng/ml), 2.44 ± 0.16 ng/ml in cohort B and 0.96 ± 0.6 in cohort C ($p < 0.001$). Mean baseline PRL levels were >20 times above normal in cohort A compared to >100 times above normal in cohorts B and C. Symptoms of hypogonadism were present in 55, 64 and 76% of men in groups A, B and C, respectively. There was a trend towards a larger tumor size in the low testosterone group ($p=0.06$). Visual fields defects at presentation were more prevalent in this cohort (C). With cabergoline, testosterone level increased from 3.91 to 6.42 ng/ml (Δ=2.51 ng/ml) in cohort A, from 2.44 to 5.63 ng/ml (Δ=3.19 ng/ml) in cohort B, and from 0.96 to 3.30 ng/ml (Δ=2.34 ng/ml) in cohort C ($p < 0.01$ for all groups). Symptoms of hypogonadism improved following treatment in 83% of symptomatic men in cohort A.

Conclusions: Normal testosterone does not exclude the likelihood of prolactinoma in men. When treated with cabergoline, testosterone levels in these men can increase higher within the normal range together with clinical improvement.

P-77

The involvement of hypothalamic CRFR1 in neurocircuits mediating energy homeostasis (ID: 89)

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Background: The arcuate nucleus (ARC) located in the mediobasal hypothalamus, plays a key role in the regulation of energy homeostasis and in the regulation of hormone secretion from the pituitary. The ARC is composed of several neuronal populations, including two major populations with opposing effect on food intake and energy expenditure. The first population co-express neuropeptide Y (NPY) and agouti-related protein (AgRP), which stimulate food intake via distinct mechanisms, while adjacent neurons that suppress food intake and favor weight loss, co-express pro-opiomelanocortin (POMC) and cocaine and amphetamine related transcript (CART). Stress has been shown to influence both humans and rodent eating behavior. The corticotropin releasing factor (CRF) neuropeptide along with its specific receptor, CRFR1, play an important role in mediating the neuroendocrine and behavioral responses to stressful challenges. CRFR1 is highly expressed in the ARC, yet, the nature and function of these neurons are still unknown.

Aim: In this study we aimed to characterize the identity of the CRFR1 expressing neurons in the ARC.

Results: To this end we used a transgenic mouse model in which the expression of GFP is based on a bacterial artificial chromosome (BAC) that contains the entire CRFR1 genomic locus (CRFR1-GFP mice). The different neuronal populations in the ARC were identified using either immunostaining or by crossing the CRFR1-GFP mice with specific mouse reporter lines using the Cre-lox system. Brain slices obtained from these mice were analyzed using confocal microscopy. Our analysis show that in the ARC, 40% of CRFR1 expressing neurons co-express AgRP, 18% co-express POMC and 20% co-express somatostatin. Additionally, we found that CRFR1 is not expressed in dopaminergic neurons.

Conclusions: In summary, we classified most of CRFR1 expressing neurons in the ARC, which provide the first essential step in elucidating the role of this stress-linked and highly expressed receptor in mediating the metabolic consequences of stressful challenges.

P-61

The role of Vasorin/ATIA in ovarian physiology (ID: 8)

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Background: The ovary is composed of follicles, each of which containing a prophase-arrested oocyte surrounded by somatic cells. Bidirectional communication between the oocyte and the somatic cells is crucial for maintenance of meiotic arrest, proper folliculogenesis, ovulation and the formation of the corpus luteum. Many of the signaling molecules involved in the dialog between the oocyte and the somatic compartment of the ovarian follicle belong to the transforming growth factor-β (TGFβ) superfamily. Among other regulatory mechanisms, TGFβ signaling is attenuated by its binding to the soluble form of Vasorin/ATIA (Vasn), a type I membrane protein, cleaved in the plasma membrane by Adam17. In addition, Vasn was found to be a hypoxia inducible factor (HIF)-1 target, which is expressed in the mitochondria and protects cells from TNFα and hypoxia-induced apoptosis. Since the ovarian follicle is scarcely vascularized and hypoxic conditions control its proper function, Vasn may also be involved in protecting ovarian cells from possible hypoxic damage in addition to its role in regulating TGFβ activity. Importantly, Vasn knockout (KO) caused impaired fertility in males due to increased testicular apoptosis and brought about infertility in female.

Aim: Our main goal is to explore the role of Vasn in ovarian physiology and unveil its effects on female fertility.

Results: We initially found that Vasn is expressed in the ovary at different stages of folliculogenesis and that its expression is up-regulated in the ovarian granulosa cells in response to luteinizing hormone (LH). We also demonstrated that the LH-induced elevation of Vasn is sensitive to EGFR and MEK1 inhibitors suggesting a mediatory role of these signaling molecules in its regulation.

Conclusions: These initial results support the hypothesis that Vasn plays a role in ovulation. Our future experiments will use Vasn KO mice for the identification of the specific role of this gene in ovarian physiology.

P-62

Transforming growth factor ß1 activation contributes to thrombospondin-1 dependent apoptotic mechanisms in the ovary (ID: 15)

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Background: Thrombospondin-1 (TSP-1) is an extracellular protein that participates in cell-matrix communication. It is a large, multi-modular protein that can exert its anti-angiogenic activities through multiple mechanisms involving different domains.

Results: Our recent studies suggested the relevance of TSP-1 to ovarian physiology demonstrating that this protein was elevated specifically in the corpus luteum that undergoes prostaglandin F2a (PG)–induced luteolysis. PG also stimulated TSP-1 in both granulosa (GCs) and luteal endothelial (LEC) cells. Yet, the biological effects of TSP-1 on luteal cells have not been well defined. We found that TSP-1 dose-dependently reduced GCs and LECs numbers under basal conditions or with FGF_2. Additionally, treatment with TSP-1 promoted LEC apoptosis, manifested by fragmentation of the nuclei and activation of caspase-3. Most of the anti-angiogenic effects of TSP-1 in cancer, including apoptosis, are associated with receptor CD36. However, mimetic peptide of TSP1 (ABT-898), that acts via the CD36 receptor, reduced only the number of viable GCs. What then is inducing apoptosis of LEC in response to TSP-1? We found that PG induced the expression of transforming growth factor ß1 (TGF-ß1) gene in luteal cells, as well as in LEC after 4h and 24h of treatment. TGF-ß1 dose dependently elevated Smad-2/3 phosphorylation in LEC. Importantly, TSP-1 too promoted phosphorylation of Smad-2/3 after 1h of treatment of LEC with 100-500 ng/ml of TSP-1, suggesting that TSP-1 induced the activation of latent TGFβ1. Since TSP-1 is highly expressed in these cells, we next studied the effects of its silencing by using siRNA molecules. These constructs effectively reduced TSP-1 gene and protein expression by approximately 70% and 85%, respectively. When TSP-1 was silenced, TGF-ß1 mRNA levels were reduced in both LEC and GCs. Furthermore, caspase-3 levels in serum-starved, TSP-1-silenced LEC were significantly reduced compared with cells transfected with scrambled siRNA.

Conclusions: Together our findings suggest that effects of TSP-1 in LEC are mediated, at least partially, via TGFβ1. TSP-1 acting via TGFβ1 and CD36 leads to apoptosis of luteal cells, thereby contributing to the regression of the corpus luteum.

P-63

Controlling cyclooxygenase-2 activity in cows follicles by RNA interference (ID: 16)

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Cyclooxygenase-2 (COX-2) is the rate limiting enzyme in prostaglandins (PGs) synthesis. It is an inducible enzyme stimulated by variety of proinflammatory cues. In ovary LH surge upregulates COX-2 where PGs play essential roles in follicular rupture and ovulation. Amongst many other genes, at the time of ovulation LH induces epidermal growth factor (EGF) - like proteins: amphiregulin (AREG) and epiregulin (EREG). The effect of LH and PGE2 in granulosa cells (GCs) quite often overlap, for instance EGF- like factors are increased following PGE2 stimulation, resembling effects of LH. Furthermore use of COX inhibitors (selective/non-selective) showed suppressed AREG and EREG despite normal LH surge. However, whether or not COX-2/PGE2 mediate LH stimulation of EGF- like factors and other ovulation associated genes remains an open question.

To resolve this issue COX-2 knockdown by specific siRNA can be used as an experimental tool. Bovine GCs provide a good cell model for in-vitro study of COX-2 silencing in relation to the ovulatory process. GCs isolated from preovulatory follicles showed low COX-2 levels. COX-2 was stimulated five folds as compared to controls when cells were preincubated with FSH (10ng/ml) and then treated with hCG (10 IU) in reduced serum levels. Interestingly, levels of COX-2 in GCs treated with forskolin (10 µM) alone were 3 times less than in FSH+hCG treatment. Transfecting GCs with two different siRNA molecules targeting COX-2 showed significant inhibition of COX-2 mRNA level by 75-80% as compared to scrambled siRNA. Steroidogenic acute regulatory protein (STAR) and cholesterol side-chain cleavage enzyme (CYP11A) were not affected indicating specificity of the silencing process.

In ongoing study we will conjugate lipophilic molecule (cholesterol) with COX-2 siRNA to enhance its efficient delivery. This will open new door in the field of therapeutic treatments and provide effective tool for studying function of target genes in ovulatory follicles in-vivo.

P-64

Role of PKC isoforms in p38MAPK activation and localization by GnRH in pituitary gonadotropes (ID: 42)

Shany Mugami, *Zvi Naor Tel Aviv University*

Background: Gonadotropin releasing hormone (GnRH) is secreted in a pulsatile manner to stimulate the synthesis and release of the glycoprotein hormones LH and FSH from pituitary gonadotropes. GnRH is therefore regarded as the key hormone of reproduction and understanding its receptor signaling is crucial for basic and clinical applications.

Methods and results: The role of PKC isoforms in GnRH-stimulated p38MAPK was examined in the 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. Gonadotropes express conventional PKCα and PKCβII, novel PKCδ, PKCε and PKCθ and atypical PKC-ι/λ. The pan PKCs inhibitor GF 109203X markedly reduced GnRH- and PMA-stimulation of p38. The use of PKCs antagonist peptide for the various PKCs has revealed that PKCα, PKCδ and PKCε mediate p38 activation by GnRH in αT3-1 while PKCβII and PKCδ are involved in p38MAPK activation by GnRH in LβT2 cells. In addition, stimulation of PMA has shown that PKCa, PKCβII and PKCδ are involved in aT3-1 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.

Conclusions: We suggest that the activated p38 may be involved in gonadotropes migration. The physiological significance of gonadotropes migration is under investigation.

P-65

AKAP4 is an ERK1/2 substrate and regulator in human spermatozoa (ID: 43)

Liat Rahamim Ben Navi, *Zvi Naor Tel Aviv University,*

Background: The mitogen-activated protein kinases (MAPK) cascade is a central signaling pathway that regulates a wide variety of cellular processes, such as proliferation, differentiation, survival, apoptosis and stress responses. One of the MAPKs is ERK1/2 that plays a crucial role in signaling pathways in general and in the pituitary-gonadal axis, in particular. We have recently reported that ERK 1/2 is a positive regulator of human spermatozoa motility and acrosome reaction.

Results: Here we describe that ERK1/2 phosphorylates A-kinase anchoring protein 4 (AKAP4), which is one of the major components of the sperm fibrous sheath and is known to be crucial for sperm motility. Furthermore, we have also found that cAMP attenuated the activation of ERK1/2 by PMA in human spermatozoa. Therefore, we decided to examine whether AKAP4 is a switch molecule that links between PKA and PKC pathways in human spermatozoa. At first we found that AKAP4 is phosphorlated by ERK1/2 in human spermatozoa and identified the phosphorylation site as threonine 265. Then we examined whether the phosphorylation of AKAP4 is important for its cellular localization. Since mature sperm do not have active transcription machinery, we used a heterologous system, i.e. in HEK293T cells expressing AKAP4. Indeed, PMA treatment led to translocation of AKAP4 from the cytosol to the Golgi in the HEK293T cells. The effect was abolished in HEK293T cells expressing AKAP4-T265A, which has a point mutation in the ERK1/2 phosphorylation site. In order to check whether AKAP4 has a role in cAMP inhibition of ERK activation by PMA, we transfected the cells with tGFP-AKAP4, or with tGFP alone as a control. We found that cAMP and a phosphodiesterase inhibitor, IBMX decreased ERK1/2 activation by PMA in the HEK293T cells expressing AKAP4, while no inhibitory effect was noticed in the tGFP expressing cells.

Conclusions: Thus, AKAP4 seems to play a role as a switch molecule that links between PKA and PKC pathways in human spermatozoa. The physiological significance of AKAP4 phosphorylation by ERK1/2 in human sperm is under investigation.

P-66

Activation and role of PI3K/AKT in MAPK activation during GnRH actions (ID: 73)

Tali Bar-Lev, *Zvi Naor, Tel-Aviv University*

Background: Gonadotropin-releasing-hormone (GnRH) is a hypothalamic decapeptide that serves as a key regulator of the reproductive system. Interaction of GnRH with its cognate receptor (GnRHR), which is a GPCR, leads to intracellular mechanisms that include PLCβ-Ca^{2+}-PKCs-MAPKs cascades to mediate the expression of LH and FSH. In the context of GnRH-induced MAPK cascades in gonadotropes the role of PI3K/AKT signaling axis remains unclear.

Results: Here we describe new insight about possible linkages between MAPKs activation and PI3K/AKT axis upon GnRH activation in αT3-1 and LβT2. First, we characterized the diverse kinetic pattern of GnRH on AKT in both cell lines and on PI3K-p85-regulatory subunit in LβT2. Second, in order to elucidate the role of PI3K in GnRH-induced MAPKs activation, we incubated αT3-1 and LβT2 cells with wortmannin (10nM and 10μM) or LY294002 (10μM and 100μM) 30min or 1h before GnRH, PMA, or EGF stimulation. We found that inhibition of PI3K resulted with acute inhibition of GnRH-induced ERK1/2 activation in a dose-dependent manner, as observed also by wortmannin on EGF in αT3-1 and with LY294002 on PMA in both cell lines, and in a pre-incubation-duration-dependent manner, since 1h pre-incubation gave robust effect than 30min in both cell lines. Furthermore, GnRH-induced JNK and p38 activation did not change with both inhibitors for 30min in both cell lines, except LY294002 inhibition of GnRH-induced JNK2 in αT3-1. Next, we tested the effect of PI3K inhibition on AKT and found a dose-dependent inhibition in IGF-induced AKT activation in both cell lines. This finding raises the assumption that the effect of wortmannin on GnRH-induced ERK1/2 activation is probably mediated by a direct mechanism. This assumption is strengthened due to that wortmannin inhibition observed also on MEK activation in LβT2. Finally, we suggest that the inhibitory effect of GnRH on AKT activity is a result of GnRH-mediated activation of PP1 and PP2A, since okadaic acid and calyculin-A aborted AKT inhibition up to 60min from GnRH stimulation. Likewise, GF109203X suspended AKT inhibition induced by GnRH suggesting that PKC is also involved in GnRH-induced AKT dephosphorylation.

Conclusions: We conclude that the involvement of PI3K/AKT axis in GnRH-induced MAPKs activation is time and cellular-context-dependent.

P-67

Outcomes of pubertal development as a function of pubertal onset age (ID: 94)

Alina German, *Clalit HMO, Ze'ev Hochberg, Rambam Medical Center*

Context: The onset of girls' puberty - thelarche (B2) and pubarche (P2) - represents critical levels of estrogen and androgen, but it is the duration and conclusion of puberty that makes a girl reproductively and socially mature.

Hypothesis: The onset age of puberty impacts on its progress and growth.

Methods: We analyzed longitudinal prospectively collected data of 659 girls from 1991-2006, considering the onset of puberty (Tanner stage B2 and P2), menarche age [M]), its duration (B2 to M and to B5 and P2 to P5) conclusion (M, B5 and P5) and growth. Data were divided into quartiles (Q) by B2 age, and we compared 1st (B2 age 8.95±0.03) to 4thQ (10.74±0.60y, P<.001, mean difference 1.79y) for puberty's duration and completion parameters.

Results: 1st Q for B2 had their P2 at age 9.81±0.65 and 4thQ at 10.74±0.77y, (P<.001, diff 0.92y), and M at 11.91±1.18 and 12.99±1.12y (P<.001 diff 1.08y). Thus, P2 lagged behind B2 by 0.86±0.65 for the 1stQ, but it was 0 (±0.79) for the 4thQ. The duration from B2 to M was longer for the 1stQ (2.95±1.19) than 4thQ (2.26±1.03, P<0.001, diff 0.69y). The completion of breast development (B5) was at age 13.96±0.96 and 14.40±0.84y for 1st and 4thQ, resp. (P<0.001, diff 0.74y), whereas P5 occurred at 13.74±0.96 and 14.39 ±0.8y, resp. (P<0.001, diff 0.65y). The duration B2 to B5 was longer in 1stQ (4.71±0.97y) than 4thQ (3.66±0.87y, P<0.001, diff 1.05y) but P2 to P5 was comparable (NS). During B2-B5, 1stQ girls grew more (24.8± 5.5cm) than 4thQ (19.9± 4.5cm, P<0.001), yet they reached similar final adult height of 164.5±6.4cm. The duration from M to B5 was comparable between 1st and 4thQ (mean 1.69 and 1.47y, NS).

Conclusions: Early thelarche predicts earlier pubarche and M, additional pubertal growth and longer breast but not pubic hair development, yet the difference between extreme B2 ages is reduced by half with respect to pubertal duration. The duration difference is established by M, with no impact of the interval from M to pubertal completion. Parents may be reassured that early B2 girls have longer puberty, comparable final height and M only three years later.

P-68

DNA methylation and hydroxymethylation play a role in the expression of the luteinizing hormone β-subunit gene (ID: 98)

Yahav Yosefzon, *Philippa Melamed, Technion-Israel Institute of Technology*

The genes encoding the hormone-specific β-subunits of luteinizing hormone (LH), and follicle stimulating hormone (FSH) are quiescent soon after birth and their expression is re-initiated at puberty following stimulation by Gonadotropin releasing hormone (GnRH).
We hypothesized that part of this GnRH action might be through overcoming DNA methylation-mediated repression of these genes. To test this, we treated two gonadotrope cell lines with an inhibitor of DNA methyltransferases. This led to an increase in LHβ expression in immature gonadotropes (αT3-1 cells) which barely express LHβ, but not in mature gonadotropes (LβT2 cells) which express LHβ at high levels. Moreover, we found that the LHβ promoter is methylated in αT3-1 cells, while in LβT2 cells there was less methylation in the region containing the major transcription factor binding sites. These results indicate that the levels of LHβ expression are related to its methylation status. Functional demethylation may be conferred by conversion of the 5-methylcytosine to a hydroxymethylcytosine (5hmC) by Tet enzymes. We tested whether 5hmC is found at the LHβ gene, and discovered that the LHβ promoter contains more 5hmC in LβT2 cells than in αT3-1 cells. Tet1 and Tet2 enzymes are down-regulated with differentiation, and, accordingly, we found that both enzymes are expressed at higher levels in the immature than the mature gonadotropes, and that GnRH alters their expression.
Collectively our results suggest that DNA methylation has a role in regulating LHβ expression and that GnRH may affect the methylation pattern, possibly through the activity of the Tet enzymes.

P-69

Management of hypogonadism in adolescent girls and adult women with Prader-Willi Syndrome (PWS) (ID: 99)

Talia Eldar-Geva, *Shaare Zedek Medical Center, Harry Hirsch, Shaare Zedek Medical Center, Varda Gross-Tsur, Shaare Zedek Medical Center.*

Background: PWS is a neurodevelopmental disorder characterized by an insatiable appetite, dysmorphic features, cognitive and behavioral difficulties and hypogonadism. Most PWS girls have amenorrhea or oligomenorrhea, however, some pregnancies have been described. The heterogeneous patterns of reproductive hormones indicate that some PWS women may suffer from symptoms of hypoestrogenism, while others may potentially be fertile. We showed that inhibin B is the most reliable indicator of ovarian function in PWS.

Objectives: To describe our experience with and propose guidelines for the management of hypogonadism in adolescent girls and adult women with PWS.

Methods: All females age ≥16 years with genetically confirmed PWS known to our clinic were included: 20 subjects (12 deletion, 7 UPD, 1 imprinting center defect), ages 27.3±7.9years. General physical examination, pubertal assessment (Tanner classification), BMI, gynecological examination and ultrasonography (when possible), bone densitometry [dual energy X-ray absorptiometry (DXA)] and hormonal profiles [FSH, LH, inhibin B (INB), estradiol, prolactin and TSH] were performed. Ovarian function (failure if INB <20pg/ml), menstrual cycles (oligo/amenorrhea or irregular bleeding), ultrasound findings (endometrial thickness, uterine/ovarian abnormalities), BMI, bone densitometry, and patient/caregivers attitude were considered in developing individualized treatment recommendations.

Results: We classified 7 women with INB>20ng/ml as potentially fertile. In some cases, especially when contraceptive or hormonal replacement treatment was recommended, our advice was not followed due to parental objections and/or poor compliance (Table 1).

Table 1: Intention to treat and actual treatment.

Treatment	Intention	Actual
Contraceptive pills	3	2
Contraceptive IUD	1	1
HRT (estrogen + progesterone)	4	1
Cyclic progesterone	1	1
Non hormonal treatment of osteoporosis / osteopenia	All	All
No indication for treatment/no treatment	11	15

We recommended the contraceptive pills for a 26 year-old woman whose INB level was 53pg/ml and FSH 6.4IU/L. This patient refused any contraception and one year later she conceived spontaneously and had an abortion.

Conclusions: Guidelines for hormonal replacement therapy in adolescent girls and adult women with PWS need to be tailored individually depending on physical development, hormonal profiles, particularly inhibin B, bone density, and emotional and social needs of each PWS adolescent and adult.

P-70

Bone age assessment by a novel quantitative ultrasound based device, SonicBone, is comparable to the conventional Greulich and Pyle method. (ID: 66)

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Background: Bone age (BA) assessment in children is based on interpretation of hand x-ray scans according Greulich and Pyle standard atlas (GP). The aim was to evaluate an ultrasound based device, SonicBone, for safety, reproducibility and concordance to the current method.

Methods: Study population included 150 participants, 74 males, mean age 10.6±3.3 years, attending pediatric endocrinology clinic. X-ray scans were evaluated independently by 4 pediatric endocrinologists according to GP. SonicBone assessments were performed by two observers. Study population was randomly divided to 2 groups. A group of 100 participants, to assess correlation between speed of sound (SOS) and distance (DIS) parameters of SonicBone and BA by GP, and to establish an algorithm for provision of a numeric BA assessment in years. A group of 50 participants to assess concordance between BA based on GP and BA based on SonicBone.

Results: The SonicBone has high repeatability performance, 0.73% relative standard deviation (RDS) for SOS and 3.5% RDS for DIS. Pearson correlation between BA by GP, SOS and DIS demonstrated a significantly high correlation in all areas. The algorithm including age, gender, SOS and DIS for each skeletal location, wrist, carpal and phalangeal, has R square of 0.87, $p<0.004$. BA by SonicBone was highly correlated with BA by GP, with R square of > 0.946 and p value <0.0001 for all locations.

Conclusion: SonicBone device is safe, convenient, non painful and highly reproducible. Its BA assessment in a population of children attending pediatric endocrinology clinics is comparable to BA by GP method.

P-71

Understanding the role of GnRH in activating transcription of LHβ gonadotropin subunit gene through its effects on nucleosomal dynamics (ID: 86)

Sergei Rudnizky, *Philippa Melamed, Lilach Pnueli, Technion - Israel Institute of Technology.*

Background: Luteinizing hormone (LH) is an anterior pituitary gonadotropin heterodimeric glycoprotein, composed of two subunits: α and β. It plays a distinct role in regulating development and function of the gonads, where the β-subunit imparts biological specificity. The synthesis and release of the LH β-subunit is positively regulated by the gonadotropin-releasing hormone (GnRH) which overcomes LHβ gene repression. To overcome this repression, the promoter region has to be accessible for the transcription machinery. Accessibility is achieved by removal of nucleosomes or repositioning of nucleosomes in the region. Various factors influence nucleosome positions including histone modifications, and transcription factor binding sites. 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 gene transcription. Additionally, it has been shown that GnRH regulates gonadotropin subunit gene transcription at the chromatin level, through displacement of histone deacetylases (HDACs), thereby allowing subsequent histone acetylation.

Results: Here, we used MNase-qPCR analysis to characterize the nucleosome positioning in the LHb promoter area in cells that do not express the LHβ gene(αT3-1) and in cells that express gene abundantly(LβT2). Additionally, we compared nucleosome enrichment patterns in both cell types without treatments, and found that the nucleosome occupancy in the region of Egr-1 and SF-1 binding sites is higher in αT3-1 than in LβT2 cells, in αT3-1 cells treated with GnRH for 8 h, as well as in αT3-1 cells treated with the HDACs inhibitor TSA (Trichostatin-A) for 24 h. We performed Chromatin Immunoprecipitation (ChIP) studies and found that SF-1 and Pitx-1, but not Egr-1 are already located on the LHb promoter in αT3-1 cells even before GnRH treatment. After 1 h of GnRH treatment, we found an increase in Egr-1 occupancy on the LHβ promoter and observed the Histone 3 acetylation on Lysine 56 (H3K56).

Conclusions: Taken together, our results suggest that transcriptional activation of the LH β-subunit gene by GnRH causes nucleosome repositioning in its regulatory region through upregulation of gene specific transcription factors and subsequent histone modifications.

P-51

Differential expression of estrogen receptors-, vitamin D receptor- and 1a - hydroxylase 25- hydroxy vitamin D mRNA in human normal thyroid vs. papillary carcinoma cells is linked to differential effects of estrogen and vitamin D on cell growth. (ID: 31)

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Background: Estrogen receptors (ER), vitamin D receptors (VDR) and 1a- hydroxylase 25-hydroxyvitamin D (1OHase) mRNA are expressed in various non-reproductive cancer cells, where they apparently modulate proliferative activity.

Aims: To explore the possibility that human papillary thyroid carcinoma (PTC) are more sensitive to estrogenic effects and/or vitamin D than normal thyroid cells.

Methods: We harvested and cultured papillary thyroid carcinoma (PTC) and adjacent normal thyroid cells obtained during total thyroidectomy from 8 patients. Gene mRNA expression of ERa, ERb, VDR and 1OHase mRNA was assessed by real time PCR and proliferation was estimated by 3[H] thymidine incorporation.

Results: Both normal thyroid and PTC cells expressed ERa, ERb, VDR and 1OHase mRNA. Normal thyroid cells had higher abundance than PTC cells of ERa (0.031+0.014 vs. 0.023+0.002 aribitrary units, [AU], $p<0.05$) and 1OHase (0.013+0.007 vs. 0.008+0.0005 AU, $p<0.05$). ERb expression was similar in both cell types. VDR mRNA was very strongly expressed in both cell types but more abundant in cancer cells than in normal thyroid cells (0.339+0.039 vs. 0.271+.03 AU, respectively, $p<0.05$). Both normal thyroid and PTC cells showed increase in DNA synthesis in response to estradiol (E2), the ERa selective agonist PPT and the ERb selective agonist DPN, but the proliferative response (relative to untreated cells) was more prominent in cultured PTC than in normal thyroid cells (220 % vs. 135 %, 230% vs. 150%, 190% vs. 130%, respectively, $p<0.01$ for all). The modified ERb ligand developed by us from daidzain, cDtboc, inhibited cell growth more effectively in PTC than in normal cells (down to 62, 48, 40% vs. 110, 75 and 65% respectively, $p<0.05$-0.01). Vitamin D non-calcemic analogs [CB, EB] inhibited cell proliferation by 30 and 48%, respectively, and these effects were not further modified by coincubation with cDtboc.

Conclusions: These results are consistent with the hypothesis that endogenous estrogens and vitamin D may affect thyroid cancer cell growth via opposing pathways: cell growth acceleration via induction of ER expression, in association with the induction of VDR and 1OHase to promote the synthesis of 1,25 which is known to inhibit cell proliferation via binding to its receptors.

P-52

Role of cytological and ultrasonographic features in predicting the risk of malignancy in thyroid nodules with indeterminate cytology (ID: 40)

Leonard Saiegh, *Endocrinology Dep. Bnai-Zion medical Center, Carmela Shechner, Gabriel Dickstein, Mohammad Sheikh-Ahmad, Maria Reut, Majed Odeh, Aurora Toubi, Jacob Bejar*

Aim: To examine the diagnostic value of several cytological and ultrasonographic features in predicting malignancy in thyroid follicular neoplasms

Methods: The sample of the study consisted of 145 patients, who have had the diagnosis of follicular neoplasm on US guided FNA, and had undergone thyroidectomy. The cytological slides and the ultrasonographic images were reviewed, and several ultrasonographic and cytological features were evaluated and correlated with final histology.

Results: Histological diagnosis of malignancy was obtained in 14.5% of the patients, papillary carcinoma being the most frequent (66% of malignancies). The cytological and ultrasonographic features that have been associated with malignancy were: micro-fragments ($P<0.00001$), overlapping ($P<0.005$), hypercellularity ($P<0.009$), micronucleoli ($P<0.013$), atypical features ($P<0.027$), nodule size larger than 2 cm ($P<0.029$) and micro-calcifications ($P<0.0002$). Using the features that were statistically independent ones, which included two cytological features: micro-fragments and micronuclei, and one ultrasonographic feature: micro-calcifications, a statistical model for predicting malignancy was constructed. According to this model, it was found that the risk for malignancy is 2.65% in the absence of the three parameters, and amounts to 93.93% in the presence of all three of them.

Conclusion: In a thyroid follicular neoplasm, the cytological and ultrasonographic features that were associated with malignancy were: micro-fragments, overlapping, hypercellularity, micronucleoli, atypical features, nodule size larger than 2 cm and micro-calcifications. In an attempt to predict malignancy, we proposed a simple statistical model using only three features derived from cytological and ultrasonographic tests.

P-53

Construction of an “ideal” thyroid cancer vector: an update (ID: 48)

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Thyroid carcinomas contribute 1% of all tumours, but 90% of endocrine-related tumours. Of all thyroid cancers, papillary thyroid carcinomas (PTC) account for approximately 85% of thyroid cancers, follicular carcinomas (FTC) 14%, and anaplastic carcinoma (APC) 1%. 20-30% of all thyroid carcinomas lead to a poor prognostic outcome, which emphasises the need for better and more targeted treatments. Identification of Adeno-associated viruses (AAV) has proven to be a relatively safe tool in gene therapy, and this has led to many clinical trials for a variety of conditions, including cancer.
In this study, we tested various AAV serotypes, including a minimal Thyroglobulin (Tg) promoter/enhancer or CMV driven eGFP reporter, as vectors for study. Testing of seven AAV serotypes, expressing CMV promoter/enhancer driven eGFP reporter, indicated that the most efficacious viral coat for PTC is AAV-12 (82.7%), for FTC the AAV hybrid serotype AAV-DJ (100%), and for ATC AAV-2 (82.1%). As stated, while fluorescence occurred in over 80% of all cells, expression of the eGFP reporter varied, as seen by differing levels of green fluorescence. Further testing with the minimal Tg promoter/enhancer, in a single serotype (AAV-DJ), displayed reduced fluorescence in all tested thyroid cancer cells (FTC 35%, ATC 7.5%, PTC 1%). Additionally, we are currently involved in identifying a toxin as the optimal tool to be driven by the minimal Tg promoter/enhancer. With alterations to the viral coat, which would also yield increased tissue specificity, our resultant vector could provide an effective new tool in the Physician's arsenal.

P-54

Simultaneous occurrence of medullary and papillary thyroid microcarcinomas: a case series and review of the literature (ID: 70)

Adnan Zaina, *Elzbieta Baron, Eldad Arad, James Dana, Yaakov Shendler*

Introduction: Papillary thyroid microcarcinoma has been demonstrated to present in association with medullary thyroid carcinoma, however, medullary thyroid carcinoma and papillary thyroid carcinoma represent a rare entities. In recent years this rarity has been increasingly observed. The pathogenesis is still controversial. Genetic analysis of RET proto-oncogenes in cases of simultaneous papillary thyroid carcinoma and medullary thyroid carcinoma has so far provided conflicting results, although it seems that germline mutations play a potential role in the development of both histological types.

Case presentations: This paper describes four rare cases of simultaneous medullary thyroid carcinoma and papillary thyroid microcarcinoma with unique features: Case one was a 43-year-old Jewish woman, born in Israel, daughter of a Latvian immigrant mother and a father born in Israel. Case two was a 44-year-old Arab woman born in Israel. Case three was a 45-year-old Jewish woman, born in Israel, daughter of Moroccan immigrant parents and is unique for the presence of lymph node metastatic medullary thyroid carcinoma, and one lymph node with metastatic papillary carcinoma found in the same side. Case four was a 77-year-old Jewish woman, born in Iraq. These cases are unique in their composition of thyroid carcinoma, consisting of histologic features of medullary thyroid carcinoma, papillary thyroid microcarcinoma, and follicular thyroid adenoma. The four cases represent different ethnicity groups that live in north Israel, and case four is notable for the advanced age of the patient (77 years).

Conclusion: These four cases add more data supporting the coincidental coexistence of papillary thyroid microcarcinoma and medullary thyroid carcinoma, our results may suggest that the simultaneous occurrence of medullary thyroid carcinoma and papillary thyroid microcarcinoma is generally a simple reflection of this coincidence. Endocrinologists and pathologists should be aware of this entity. The pathologist can play a pivotal role in identifying papillary thyroid microcarcinoma in concurrent existence with medullary thyroid carcinoma.

P-55

The role of radionuclide imaging in evaluation of thyroid nodules with indetermined cytology (ID: 77)

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Introduction: Thyroid nodules with indeterminate cytology (IC) [Bethesda 3-4] represent about 15 % of all thyroid FNA results. Most of these nodules are surgically removed with risk of malignancy being 15-30%. In light of this data, identification of very low risk patients in this clinical setting can prevent unnecessary surgery. Low risk nodules tend to express higher amounts of NIS protein than the extranodular thyroid tissue, thus appearing as 'hot' nodules on I123 scans. These nodules also tend to have less metabolic activity, i.e., less mitochondrial activity. A Tc-99m MIBI scan [MIBI] represents cellular mitochondrial activity. Few studies have evaluated the MIBI scan as a tool for work up of IC nodules. The negative predictive value of this test in excluding malignant nodules is high (95%). However, it is not routinely used

Aim: The aim of this study was to evaluate the contribution of radio-nucleic imaging, based on these 2 thyroid cell characteristics, in the assessment of IC nodules.

Methods: Eighteen patients (3 men and 15 women, aged 52±15) with IC nodules were included in the study, in 2010-2012. Because the I123 scan is not available in Israel, it was replaced by the Tc-99m pertechnate (Tc scan). All patients underwent Tc scan. Patients with ‘hot’ nodules on regular or post-levothyroxin suppressive therapy were followed. A MIBI scan was offered to patients with a Tc scan 'cold' nodule, who initially did not accept surgery as a treatment option.

Results: Two patients who had 'hot' nodules on Tc scan and three patients, who had ‘cold’ nodules on MIBI scan, were offered surveillance. During 12 to 36 months follow up, no clinical and ultrasonographic changes occurred in these patients. Nine patients with ‘hot’ MIBI nodules underwent surgery. Four of them had malignancy. Four patients with 'non-hot' Tc and 'hot' MIBI scan nodules refused surgery and were followed for 6 to 12 months, with stable ultrasonographic characteristics.

Conclusions: This protocol defines low malignancy risk in 28% patients with IC and thus, prevented unnecessary surgery. Larger studies with longer follow-up are needed to validate the long-term consequences of an active-surveillance policy in this unique subgroup.

P-56

The effect of hypothyroidism on surgical outcome of patients with hip fractures (ID: 82)

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Introduction: Thyroid dysfunction is a common endocrinopathy, affecting 4.3% of the population, particularly women and older patients. Hypothyroidism may depress myocardial function, decrease ventilation, cause anemia and impair hepatic drug metabolism. Thyroid dysfunction may be particularly challenging in the management of the surgical patient.

Aim of the study: To evaluate the effect of uncontrolled hypothyroidism on surgical outcome of patients with hip fractures having emergent surgery.

Methods: A retrospective study of patients that had emergent hip surgery at Meir Medical Center during 1/2010 and 07/2011. Data collected from charts included demographic data, previous medical history, laboratory tests, surgical procedure, perioperative morbidity and mortality and long term mortality. A TSH > 4 mU/L was defined as hypothyroidism. A matched controlled group of euthyroid patients was chosen.

Results: A total of 640 records of patients that underwent surgery due to hip fracture were reviewed. A total of 45 patients with a TSH > 4 mU/L in the perioperative period were found. The mean age was 83.7y ± 9.3 and 83.7y ± 9 (P=0.99) in the hypothyroid and control group respectively. Mean TSH was 11.2 mU/L ± 20.1 in hypothyroid patients and 1.8 mU/L ± 0.7 in the control group (P=0.016). In the hypothyroid group, 95% had a diagnosis of hypothyroidism. A preoperative diagnosis of anemia and arrythmia was more common in hypothyroid patients (24.4% vs 8.9%,P=0.048 for anemia and 33.3% vs 13.3%, P=0.025 for arrythmia). Hypothyroid patients had more episodes of hypotension compared to the control group (64.4% vs 33.3%, P=0.003) and needed more blood transfusions (1.8 units vs 1.3 units, P=0.044) during surgery. The length of hospitalization, the complication rate of ileus, need for mechanical ventilation, arrythmia, cardiovascular complications, infection rate and mortality was similar between groups.

Conclusion: Hypothyroid patients that underwent emergent surgery due to hip fractures had a higher rate of intraoperative hypotension and needed more blood transfusions compared to euthyroid patients.

P-57

Falsely normal ACTH level in ectopic Cushing's syndrome due to interfering antibodies (ID: 37)

Leonard Saiegh, *Endocrinology Dep. Bnai-Zion medical Center, Limor Chen-Konak, Mohammad Sheikh-Ahmad, Maria Reut, Carmela Shechner*

Introduction: A woman presented with ectopic Cushing's syndrome (CS). Plasma ACTH levels were normal, but elevated when measurement was performed after multiple dilutions or after extraction of interfering antibodies.

Background: Normal plasma ACTH level in severe ectopic CS caused by large gastric neuroendocrine tumors is rare. In such cases, one would suspect that the severe clinical and biochemical CS is due to the presence of high levels of biologically active ACTH precursors. Nevertheless, as encountered with other hormone level determination by immunoassay, assay interference by antibodies giving falsely low levels should always be kept in mind. Some common ways to identify assay inference include: 1) Using a different immunoassay methods, 2) Assay sample with dilution, in which case if nonlinear response is encountered, it indicates antibody interference, 3) Using antibody blocking tubes, and 4) Using the chromatography methods (not available in Israel for ACTH).

Clinical Case: A 36 year-old woman, presented with recent weigh gain, face and legs swelling, hirsutism and abdominal pain. Computed Tomography revealed a large gastric mass with retroperitoneal involvement. Biopsy was consistent with neuroendocrine tumor stained positively for ACTH. Urinary free cortisol 5130mcg/day (N up to 115mcg/day), serum cortisol 104mcg/dl (N 5-25mcg/dl). Overnight dex.supp.test 8mg cortisol 89mcg/dl. ACTH levels in different samples were 5.3-6.9pmol/l (N: 1.1-10pmol/l), after sample dilution 1:10 ACTH level was 49pmol/l, dilution 1:20 was 67pmol/l, dilution 1:100 was ND (done by chemiluminescent immunoassay). Similar results were obtained with different samples and when measured in another Lab using the same assay. ACTH level after extraction of heterophilic and nonspecific antibodies was 19pmol/l. ACTH spiking showed 69% recovery consistent with assay interference. ACTH level conducted by Elisa at the University of Manchester using mouse IgG was 36pmol/l (N up to 22pmol/l), ACTH precursor concentration was not elevated 78pmol/l (N up to 100pmol/l).

Conclusion: To the best of our knowledge, this is the first case reported describing falsely normal ACTH level due to interfering antibodies in an ectopic CS. Therefore, when an ectopic CS is suspected but, ACTH levels are normal and results in dynamic tests are inconsistent, we recommend ruling out interfering antibodies.

P-58

Clinical follow-up in girls with non-classical congenital adrenal hyperplasia: Can oral contraceptives replace steroid treatment? (ID: 65)

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Background: Steroid therapy effectively suppresses elevated androgen levels associated with non-classical adrenal hyperplasia (NCCAH), but it may induce side effects and make patients unfit for army service. Therefore, some doctors replace steroids with oral contraceptives (OC) in girls who have completed linear growth. The medical literature on the efficacy of oral contraceptives in NCCAH is limited.

Objective: To determine whether the transition from steroids to OC causes changes in clinical manifestations, androgen levels or metabolic parameters.

Methods: A retrospective study of girls with NCCAH who either continued steroid therapy (n=32) or switched to OC (n=12) after completing puberty and growth. The medical records were reviewed for clinical and laboratory parameters measured before the change in medication (at 17.6±2.3 years for the steroid-treated (St) group, and 18.7±2.3 years for the OC group) and on 3 subsequent visits during the following 2 years. Findings were compared over time and between groups.

Results: At baseline, there were no significant between-group differences in BMI-SDS, androgen hormone levels or prevalence of clinical polycystic ovary. The percentage of patients in the St and OC groups who presented with acne, hirsutism and irregular menses was 53% vs 50% (p=0.6), 54% vs 36.4% (p=0.27) and 3.1% vs 16.7% (p=0.2), respectively. Over time, there was no significant difference in the severity or prevalence of acne or hirsutism in either group or between groups. The menstrual cycle became regular in all patients treated with OC's, with no change in St group (96.9%). Increase in androstendione from mid-range to upper limit of normal or slightly above was observed in the OC group, and a trend of weight reduction, but the differences from the St group were not statistically significant. No significant differences in BMI-SDS, systolic and diastolic blood pressure, fasting glucose levels and lipid profile were found between groups at baseline and during follow-up.

Conclusions: In girls with NCCAH who complete growth, replacement of steroid therapy by oral contraceptives leads to regular menses, with no worsening of acne or hirsutism despite a trend of increased androstenedione levels. Larger prospective, randomized studies, with longer follow-up are required to corroborate our findings.

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List of posters by groups

Posters: Diabetes, Obesity and Metabolism

Group A

Date: Tuesday, April 9, 2013
Time: 11:15 AM - 12:30 PM
Location: Patio (outside the Bareket hall)
Session Chair: Hannah Kanety
Session Chair: Anat Tzur

[P1] The efficacy of using the Internet-based CareLink® Therapy Management System for diabetes in patients with type 1 diabetes (T1D) (ID: 6)

[P2] New Onset Diabetes Mellitus in Elderly Subjects: Association between HbA1c Levels, Mortality and Coronary Revascularization (ID: 12)

[P3] Basal-bolus insulin versus sliding scale insulin in management of inpatients with type 2 diabetes: a prospective randomized controlled study. (ID: 20)

[P4] Impaired decline in Renal Threshold for Glucose during pregnancy– A possible novel mechanism for Gestational Diabetes Mellitus (ID: 21)

[P5] Do adiponectin levels explain the atherogenic properties of Hp 2-2 phenotype in type 2 diabetic patients? (ID: 29)
Marina Shargorodsky

[P6] Long duration of hyperglycemia in the first 96 hours of life is associated with severe intraventricular hemorrhage in preterm infants (ID: 51)

[P7] Obesity is associated with lower basal state cortisol, and diminished cortisol response to the low dose 1ug ACTH: time to depart from the obesity/pseudo-Cushing myth (ID: 60)

[P8] Autocrine function of adiponectin during differentiation: a healthy adipocyte is born (ID: 62)

[P9] Diabetic Neuropathic Cachexia: Challenges and Priorities of Clinical Practice; A case report. (ID: 69)

[P10] The role of hypercholesterolemia on cancer risk and cancer-related mortality (ID: 72)

[P11] Predictors of Resting Metabolic Rate in Healthy Obese Children Aged 5-11 (ID: 76)

[P12] Ethiopian Jews immigration to Israel in terms of diabetes mellitus outcomes (ID: 80)

[P13] Sexual dimorphism in the weight loss achieved in the treatment of the metabolic syndrome: Women do better, again… (ID: 81)

[P14] Pre-existing dysglycemia is a negative predictor of weight loss achieved in a multidisciplinary intervention program in non-diabetic women with the metabolic syndrome (ID: 83)

[P15] Hepatitis in an infant treated with octreotide for congenital hyperinsulinism (ID: 88)

[P16] Estradiol-17β enhances pancreatic beta cell proliferation through different estrogen receptors in a glucose dependent manner (ID: 91)

[P17] Gender and age, but not obesity, affects serum dexamethasone and/or cortisol levels post overnight 1 mg dexamethasone suppression test (ID: 93)

[P18] GTF - an anti diabetic material extracted from yeast decreases high glucose damages in endothelial cells (ID: 103)

[P19] High prevalence of obesity in children in Northern Israel (ID: 107)

Posters: GH, IGFs and Cancer

Group B

Date: Tuesday, April 9, 2013
Time: 11:15 AM - 12:30 PM
Location: Main Hall - Back Left Side
Session Chair: Yossi Levy
Session Chair: Simona Grozinsky-Glasberg

[P21] THE EFFICIENCY OF INTRAOSSEOUS HUMAN GROWTH HORMONE ADMINISTRATION: A FEASIBILITY PILOT STUDY IN A RABBIT MODEL (ID: 7)

[P22] HDAC10 IS INVOLVED IN FOOD RESTRICTION- INDUCED GROWTH ARREST (ID: 9)

[P23] IDENTIFICATION AND CHARACTERIZATION OF A NOVEL INSULIN- LIKE GROWTH FACTOR 1 RECEPTOR GENE HETEROZYGOUS MUTATION IN A CHILD WITH GROWTH FAILURE (ID: 18)

[P24] VALPROIC ACID IN COMBINATION WITH CHEMORADIOTHERAPY USING GEMCITABINE FOR ENHANCED TREATMENT OF PANCREATIC CANCER (ID: 22)

[P25] The effect of Leptin administration on mammary tumor growth in diabetic mice. (ID: 26)

[P26] REGULATION OF IGF1R GENE EXPRESSION AND ACTION BY THE ANDROGEN-REGULATED FUSION PROTEIN TMPRSS2-ERG IN PROSTATE CANCER (ID: 33)

[P27] IDENTIFICATION OF TUMOR PROTECTING PATHWAYS IN LARON SYNDROME PATIENTS (ID: 36)

[P28] Identification of BRCA1 as a biomarker for IGF-IR targeted therapy in breast cancer (ID: 39)

[P29] Growth Patterns In Congential Multiple Pituitary Hormone Deficiencies (Mphd) Compared To That Of Mphd Following Abnormal Delivery (ID: 49)

[P30] NON-FUNCTIONAL PANCREATIC NEUROENDOCRINE TUMORS WITH TRANSFORMATION TO INSULINOMA: AN ESOTERIC PRESENTATION OF A RARE DISEASE (ID: 74)

[P31] Carotenoids and their derivatives inhibit IGF-I activity in breast cancer cells but enhance it in bone cells. (ID: 102)

Posters: Bone, Vitamin D and Calcium Metabolism
Group C

Date: Tuesday, April 9, 2013
Time: 11:15 AM - 12:30 PM
Location: Bareket Hall - Left
Session Chair: Zaki Kraiem
Session Chair: Jonathan Arbelle

[P41] Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. (ID: 28)

[P42] Vitamin D deficiency among physicians in Israel: a comparison between hospitalists and community based physicians. (ID: 34)

[P43] Bone Density and Vitamin D Status in Liver Transplant Patients 10 Years After the First Assessment (ID: 38)

[P44] Gigantomastia and Hypercalcemia in a Pregnant Woman with Myasthenia Gravis (ID: 64)

[P45] Results of Secondary Fracture Prevention Program in Patients with Severe Osteoporosis in Rambam Health Care Campus (ID: 71)

[P46] Hypoparathyroidism and Central Diabetes Insipidus: A Search for the Link (ID: 84)

[P47] Parathyroid surgery:preoperative localization studies in correlation with the

[P48] Identifying the threshold for vitamin D deficiency in relation to health indicators (ID: 95)

[P49] Atypical fractures of the femoral shaft - is there thicker cortex present? (ID: 97)

[P50] Pseudohypoparathyroidism: clinical, molecular characteristics and long term

Posters: Thyroid and Adrenal
Group C

[P51] Differential expression of estrogen receptors-, vitamin D receptor- and 1a -hydroxylase 25- hydroxy vitamin D mRNA in human normal thyroid vs. papillary carcinoma cells is linked to differential effects of estrogen and vitamin D on cell growth. (ID: 31)

[P52] Role of Cytological and Ultrasonographic Features in Predicting the Risk of Malignancy in Thyroid Nodules with Indeterminate Cytology (ID: 40)

[P53] Construction of an “ideal” thyroid cancer vector: an update (ID: 48)

[P54] Simultaneous occurrence of medullary and papillary thyroid microcarcinomas: a case series and review of the literature (ID: 70)

[P55] THE ROLE OF RADIONUCLIDE IMAGING IN EVALUATION OF THYROID NODULES WITH INDETERMINATE CYTOLOGY (ID: 77)

[P56] The Effect of Hypothyroidism on Surgical Outcome of Patients with Hip Fractures (ID: 82)

[P57] Falsely Normal ACTH Level in Ectopic Cushing's Syndrome due to Interfering Antibodies (ID: 37)

[P58] Clinical follow-up in girls with non-classical congenital adrenal hyperplasia: Can

Posters: Reproduction and Puberty

Group D

Date: Tuesday, April 9, 2013
Time: 11:15 AM - 12:30 PM
Location: Bareket Hall - Back Right Side
Session Chair: Itzik Koch
Session Chair: Simona Grozinsky-Glasberg

[P61] The Role of Vasorin/ATIA in Ovarian Physiology (ID: 8)

[P62] Transforming Growth Factor ß1 Activation Contributes to Thrombospondin-1 Dependent Apoptotic Mechanisms in The Ovary (ID: 15)

[P63] CONTROLLING CYCLOOXYGENASE-2 ACTIVITY IN COW'S FOLLICLES BY RNA INTERFERENCE (ID: 16)

[P64] Role of PKC isoforms in p38MAPK activation and localization by GnRH in pituitary gonadotropes (ID: 42)

[P65] AKAP4 is an ERK1/2 substrate and regulator in human spermatozoa (ID: 43)

[P66] ACTIVATION AND ROLE OF PI3K/AKT IN MAPK ACTIVATION DURING GnRH ACTIONS (ID: 73)

[P67] OUTCOMES OF PUBERTAL DEVELOPMENT AS A FUNCTION OF PUBERTAL ONSET AGE (ID: 94)

[P68] DNA METHYLATION AND HYDROXYMETHYLATION PLAY A ROLE IN THE EXPRESSION OF THE LUTEINIZING HORMONE β-SUBUNIT GENE (ID: 98)

[P69] Management of Hypogonadism in Adolescent Girls and Adult Women with Prader Willi Syndrome (PWS) (ID: 99)

[P70] Bone age assessment by a novel quantitative ultrasound based device, SonicBone, is comparable to the conventional Greulich and Pyle method. (ID: 66)

[P71] UNDERSTANDING THE ROLE OF GnRH IN ACTIVATING TRANSCRIPTION OF THE LHβ GONADOTROPIN SUBUNIT GENE THROUGH ITS EFFECTS ON NUCLEOSOMAL DYNAMICS (ID: 86)

Posters: Neuroendocrinology

Group D

[P72] Insulin/IGF-1-Induced Epigenetic Changes in the Brain (ID: 46)
raz shperling

[P73] Clinical Course and Outcome of Non-Functioning Pituitary Adenomas in the Elderly Compared with Younger Age Groups (ID: 54)

[P74] Non-functioning Pancreatic Neuroendocrine Tumors (PNET): Association with Prediabetes/Diabetes (ID: 56)

[P75] KISS1 receptor is preferentially expressed in clinically non-functioning pituitary tumors and does not correlate with tumor size or invasiveness (ID: 57)

[P76] Male Prolactinomas Presented with Normal Testosterone Levels (ID: 58)

[P77] The involvement of hypothalamic CRFR1 in neurocircuits mediating energy homeostasis (ID: 89)

Posters location