PROGRAM BOOK

ברוכים הבאים

הכנס ה- 49 של האגודה הישראלית לאנדוקרינולוגיה

חברי אגודה ומשתתפים יקרים!

אנו שמחים לראות אתכם כאן אתנו בכנס המדעי. בגין המגיפה הכנס נדחה ועבר לפלטפורמה הדיגיטלית. לשמחתנו המרצים מהארץ ומחו"ל הסכימו להשתתף גם באופן הזה ואנו מודים להם על כך.

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אנו רוצים להודות לכל מי שתרם להצלחת הכנס ובמיוחד לפרופ' רות שלגי שפעלה רבות בבניית תכני הכנס במועדו המקורי, לדוברים ולמציגי התקצירים שטרחו להכין מראש את ההרצאות ולשלוח אותן, לחברת פראגון על ארגון התהליך וליוויו, ולחברות התומכות בפעילות האגודה.
אנו מקווים שתיהנו מהתכנים ומנוחות השימוש בפלטפורמה. התכנים המוצגים יהיו זמינים גם במהלך שלושת החודשים הקרובים. כולנו תקווה שבשנה הבאה נוכל להתראות פנים אל פנים.
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Sunday, December 6, 2020

09:00-10:00 Plenary Lecture 1

Chair: Gil Leibowitz Lev

09:00 **Introduction**
Gil Leibowitz Lev

09:10 **Inflammation in the Pathophysiology and Therapy of Diabetes and Associated Diseases**
Marc Donath
University Hospital, Basel, Switzerland

09:50 **Q&A**

10:00-10:05 Short Break

10:05-11:45 Symposium 1- Immunometabolism in Obesity and Diabetes

Chair: Gil Leibowitz Lev

10:05 **Postprandial Hypoglycemia after Gastric Bypass: Mechanisms and Treatment with SGLT2 or IL-1 Inhibition**
Marc Donath
University Hospital, Basel, Switzerland

10:30 **Inter-Cellular Communication and Propagation of ER Stress in Obesity**
Amir Tirosh
Institute of Endocrinology, Chaim Sheba Medical Center, Tel-Hashomer, Israel Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

10:55 **A Trail for Understanding OrAD (Obesity-related Adipose tissue Disease), and its Potential to Personalize Care of the Patient with Obesity**
Nitzan Maixner and Assaf Rudich
The Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences and the National Institute of Biotechnology in the Negev (NIBN), Ben-Gurion University of the Negev, Israel

11:25 **Panel Discussion and Q&A**

11:45-12:00 Break- Visit the Exhibition

12:00-13:30 Symposium 2- Diabetes in Pregnancy- Update 2020

Chair: Yoel Toledano

12:00 **Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Glycemia and Childhood Metabolic Outcomes**
Yael Lebenthal
Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Israel

12:25 **MicroRNAs in Gestational Diabetes Mellitus and Preeclampsia**
Noam Shomron
Sackler Faculty of Medicine, Sackler Faculty of Medicine, Tel Aviv University, Israel

12:50 **Pregestational Diabetes- Improving Pregnancy Outcomes: State of the Art 2020**
Elisabeth R Mathiesen
University of Copenhagen, Copenhagen, Denmark

13:15 **Panel Discussion and Q&A**

13:30-14:10 Break- Visit the Exhibition

14:10-15:30 Short Oral Presentations- Adrenal Thyroid

Chair: Karen Tordjman

14:10 **Persistent Medullary Thyroid Carcinoma: An Israeli Multicenter Study**

Shlomit Koren[1,7], Miriam Shteinshneider[1,7], Orit Twito[2,7], Simona Glasberg[3], Dania Hirsch[4,7], Gideon Bachar[5,7], Carlos Benbassat[1,7], Limor Muallem Kalmovich[1,6,7]
[1]*Endocrine Institute, Assaf Harofeh Medical Center, Israel*
[2]*Institute of Endocrinology, Meir Medical Center, Israel*
[3]*Neuroendocrine Tumor Unit, Endocrinology & Metabolism Service, Hadassah-Hebrew University Medical Center, Israel*
[4]*Institute of Endocrinology, Rabin Medical Center, Israel*
[5]*Department of Otorhinolaryngology, Rabin Medical Center,, Israel*
[6]*Department of Otorhinolaryngology, Assaf Harofeh Medical Center, Israel*
[7]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

14:20 **Increased BMI is Associated with Anti PD-1/PD L1-Induced Thyroid Immune-Related Adverse Events**

Amit Ashash, Rivka Dresner-Pollack, Avivit Cahn, Rena Pollack
Department of Endocrinology and Metabolism, Hadassah Medical Center, Israel

14:30 **Subclinical Hypothyroidism in Pregnancy – Do Different TSH Cutoffs Predict Peripheral Hormones Change?**

Gilad Karavani[1], Lina Daoud-Sabag[1], David Strich[2], Cherut Chay[3]
[1]*Obstetrics and Gynecology, Hadassah-Hebrew University Medical Center, Israel*
[2]*Pediatric Specialist Clinic, Clalit Health services, Jerusalem District and Pediatric Endocrinology Unit, Shaare Zedek Medical Center, Israel*
[3]*Rabin Medical Center, Petach Tikva, Israel*

14:40 **Cushing's Syndrome (CS) in the 21st Century, not what it used to be: A Single Institution Experience**

Arza Rosset, Yona Greenman, Gabi Shefer, Etty Osher, Naftali Stern, Karen Tordjman
Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel

14:50 **Q&A**

14:10-15:30 Short Oral Presentations- Bone Metabolism

Chair: Galia Gat-Yablonski

14:10 **Denosumab Associated Risk of Malignancy- systematic Review and Meta-analysis of Randomized Controlled Trials**

Dana Rosenberg[1,3], Tomer Avni[1,3], Gloria Tsvetov[2,3], Anat Gafter-Gvili[1,3], Talia Diker-Cohen[1,2,3]
[1]*Medicine A, Rabin Medical Center - Beilinson Hospital, Israel*
[2]*Institute of Endocrinology, Diabetes and Metabolism, Rabin Medical Center - Beilinson Hospital, Israel*
[3]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

14:20 **Burosumab Therapy in Children and Adolescents with X-linked Hypophosphatemia: The Real-life Israeli Experience**

Leonid Zeitlin[1,2], Shelly Levi[2,3], Shoshana Gal[4,5], Avivit Brener[2,6], Yael Lebenthal[2,6], David Gillis[7,8], David Strich[8,9], Amnon Zung[8,10], Roxana Cleper[2,11], Yael Borovitz[2,3], Zvi Zadik[8,10], Miriam Davidovits[2,3], Yael *Levy-Shraga[2,12], Dov *Tiosano[4,5]
[1]*Pediatric Orthopedic Department, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Israel*
[2]*The Sackler Faculty of Medicine, Tel-Aviv University, Israel*
[3]*Pediatric Nephrology Unit, Schneider Childrens Medical Center, Israel*
[4]*Division of Pediatric Endocrinology, Ruth Rappaport Children's Hospital, Rambam Medical Center, Israel*

[5]*Bruce Rappaport Faculty of Medicine, Technion, Israel*
[6]*Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Israel*
[7]*Pediatric Endocrinology Unit, Hadassah-Hebrew University Medical Center, Israel*

[8]*Hadassah Medical School Faculty of Medicine, Hebrew University of Jerusalem, Israel*
[9]*Department of Pediatrics, Shaare Zedek Medical Center, Israel*
[10]*Department of Pediatrics, Kaplan Medical Center, Israel*
[11]*Pediatric Nephrology Unit, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Israel*
[12]*Pediatric Endocrinology Unit, The Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Israel*

14:30 **Q&A**

14:45 **The Protective Effect of Carotenoids, Polyphenols and Sex Hormones on Skin Cells under Oxidative Stress Conditions**

Aya Darawsha, Marina Hanin, Hilla Ovadia, Joseph Levy, Yoav Sharoni
Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Israel

14:55 **Cartilage Specific K/O of SIRT1 Significantly Affects Bone Quality and Inhibits Catch Up Growth**

Biana Shtaif[2,3], Meytal Bar-Maisels[1], Yankel Gabet[3], Sahar Hiram-Bab[3], Moshe Phillip[1,2,3], Galia Gat-Yablonski[1,2,3]
[1]*Endocrinology and Diabetes, Schneider Children's Medical Center, Israel*
[2]*Felsenstein Medical Research Center, Tel Aviv University, Israel*
[3]*Sackler School of Medicine, Tel Aviv University, Israel*

15:05 **The Effect of RANKL on Differentiation of Murine Bone Marrow Mesenchymal Stem Cells to Adipocytes**

Noa Hallak, Irina Gurt, Rivka Dresner-Pollak
Endocrinology and Metabolism Department, Division of Medicine, Institute of Medical Research Israel-Canada, Hebrew University-Hadassah Medical School, Israel

15:15 **Q&A**

14:10-15:30 Short Oral Presentations- Diabetes 1

Chair: Elena Izkhakov

14:10 **Reversal of Diet-induced Hepatic Steatosis by Peripheral CB1 Receptor Blockade is miRNA-22/SIRT1/PPARα Dependent**

Shahar Azar[1], Shiran Udi[1], Adi Drori[1], Rivka Hadar[1], Kiran V. Vemuri[2], Maya Miller[3], Dana Sherill-Rofe[3], Devorah Gur-Wahnon[4], Xiaoling Li[5], Alexandros Makriyannis[2], Yuval Tabach[3], Iddo Z. Ben-Dov[4], Joseph Tam[1]
[1]*Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Israel*
[2]*Center for Drug Discovery, Northeastern University, USA*
[3]*Department of Developmental Biology and Cancer Research, The Institute for Medical Research Israel-Canada, Hadassah Medical School, The Hebrew University of Jerusalem, Israel*
[4]*Laboratory of Medical Transcriptomics, Department of Nephrology, Hadassah-Hebrew University Medical Center, Israel*
[5]*Laboratory of Signal Transduction, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, USA*

14:20 **Macrophage JAK2 Deficiency Accelerates Atherosclerosis through Defects in Cholesterol Efflux**

Idit Dotan[1,2], Jiro Ikeda[1], Ziv Roth[3], Helen Le[1], Harsh Desai[1], Tharini Sivasubramaniyam[1], Evan Pollock-Tahiri[1], Sonia Rehal[1], Josh Rapps[1], Edouard Alchami[1], Changting Xiao[1], Saraf Karim[1], Marcela Gronda[4], Michael Saikali[5], Aaron Schimmer[4], Vikas Gupta[4], Mark Minden[4], Carolyn Cummins[5], Gary Lewis[1], Clinton Robbins[1], Sergio Grinstein[3], Jenny Jongstra-Bilen[1], Myron Cybulsky[1], Minna Woo[1,6]
[1]*Toronto General Hospital Research Institute, University Health Network, Canada*
[2]*Institute of Endocrinology, Beilinson Hospital, Israel*
[3]*Program in Cell Biology, Peter Gilgan Centre for Research and Learning, Hospital for Sick Children, Canada*
[4]*Princess Margaret Cancer Center, University Health Network, Canada*
[5]*Department of Pharmaceutical Sciences, University of Toronto, Canada*

[6]*Division of Endocrinology and Metabolism, Department of Medicine, University Health Network and Sinai Health System, University of Toronto, Canada*

14:30 **Proximal Tubule mTORC1 Is a Central Player in the Pathophysiology of Diabetic Nephropathy and its Correction by SGLT2 Inhibitors**

Aviram Kogot-Levin[1], Liad Hinden[2], Yael Riahi[1], Tal Israeli[1], Erol Cerasi[1], Joseph Tam[2], Ofri Mosenzon[1], Gil Leibowitz[1]
[1]*Diabetes Unit and Endocrine Service, Hadassah-Hebrew University Medical Center, Israel*
[2]*Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Israel*

14:40 **Q&A**

14:50 **The Relationship between Glucose Control & Cognitive Function in People with Diabetes after a Lacunar Stroke**

Tali Cukierman-Yaffe[1,2], Leslie McClure[3], Thomas Risoli[4], Jackie Bosch[5,6], Hertzel Gerstein[5], Oscar Benavente[7]
[1]*Endocrinology Division, Sheba Medical Center, Israel*
[2]*Epidemiology, Sackler School of Medicine, Tel-Aviv University, Israel*
[3]*Department of Epidemiology & Biostatistics Dornsife School of Public Health, Drexel University, USA*
[4]*Duke CTSI Biostatistics, Epidemiology and Research Design (BERD) Methods Core, Duke University School of Medicine, USA*
[5]*Population Health Research Institute,, Hamilton Health Sciences and McMaster University, Canada*
[6]*School of Rehabilitation Sciences, McMaster University, Hamilton, Canada, Canada*
[7]*Department of Medicine, Division of Neurology, University of British Columbia, Canada*

15:00 **The Effect of PCSK9 Inhibitor EVOLOCUMAB on Aldosterone among High Cardiovascular Risk Patients**

Elena Izkhakov[1,3], Yakov Shacham[2,3], Marianna Yaron[1,3], Merav Serebro[1,3], Karen Tordjman[1,3], Yona Greenman[1,3], Naftali Stern[1,3], Tomer Ziv[3]
[1]*Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel*
[2]*Cardiology Department, Tel Aviv Sourasky Medical Center, Israel*
[3]*Tel Aviv University, Tel Aviv, Israel*

15:10 **Symptomatic and Asymptomatic Hypoglycemia Post Three Different Bariatric Procedures: A Common and Severe Complication**

Li Or Lazar[1], Shimon Sapojnikov[1], Guy Pines[1], Eli Mavor[1], Viviana Ostrovsky[2], Tal Schiller[2], Hilla Knobler[2], Taiba Zornitzki[2]
[1]*Surgery Department, Kaplan Medical Center, Hebrew University Medical School, Jerusalem, Israel*
[2]*Diabetes, Endocrinology and Metabolic Disease Institute, Hebrew University Medical School, Jerusalem, Israel*

15:20 **Q&A**

15:30-16:00 IES Mentor Awards

Best Mentor Prize: Prof. Nava Dekel; Dr. Anat Yaffe

Best Community Physician Prize: Dr. Jonny Arbel

16:00-17:00 Plenary Lecture 2

Chair: Liat de Vries

16:00 The Genetic Investigation of a Patient with DSD

Kenneth McElreavey

Human Developmental Genetics, Institut Pasteur de Paris, Paris, France

16:45 Q&A

17:00-17:15 Break- Visit the Exhibition

17:15-18:45 Symposium 3- Update in Neuroendocrine Tumors=

Chair: Simona Glasberg

17:15 Enhancer Signatures Stratify and Predict Outcomes of Non-Functional Pancreatic Neuroendocrine Tumors

Yotam Drier

Hebrew University, Faculty of Medicine, Jerusalem, Israel

17:40 Neuroendocrine Tumors: From Diagnosis to Theranostics – What`s in the Pipeline

Guillaume P. Nicolas

University Hospital Basel, Basel, Switzerland

18:05 Current Management of Pheochromocytoma/Paraganglioma: a Guide for the Practicing Clinician in the Era of Precision Medicine

Karel Pacak

Eunice Kennedy Shriver, NICHD, NIH, Rockville, USA

18:30 Panel Discussion and Q&A

19:00-20:00 Plenary Lecture 3

Chair: Avraham Karasik

19:00 Is GLP-1 an Immunoregulatory Peptide?

Dan J. Drucker

The Department of Medicine, Lunenfeld-Tanenbaum Research Institute, Mt. Sinai Hospital, University of Toronto, Toronto, Canada

19:40 Q&A

Monday, December 7, 2020

08:00-11:00 Industry Session 1

08:00 **Sponsored by Novonordisk: New Insights on Renal Protection with GLP-1RA**

Ofri Mosenzon
Israel

08:20 **Sponsored by Novonordisk: Time to change - Time in Range**

Eytan Roitman
Israel

08:40 **Sponsored by Neopharm Israel: Timely Matters in Parathyroidism**
Moderator: Rivka Dresner Pollak , Head Department of Endocrinology and Metabolism, Hadassah-Hebrew University Medical Center

John P. Bilezikian
Silberberg Professor of Medicine, USA
Vice-Chair, Department of Medicine for International Research and Education, USA
Chief, Emeritus, Endocrinology and Metabolic Bone Diseases Units, USA
Vagelos College of Physicians and Surgeons Columbia University, USA

09:00 **Sponsored by Medison: Medical Treatment Landscape for Uncontrolled Acromegaly**

Ilan Shimon
Director, Institute of Endocrinology, Diabetes & Metabolism Professor of Medicine and Associate Dean, Sackler Faculty of Medicine, Tel-Aviv University Rabin Medical Center, Beilinson Campus, Israel

09:20 **Sponsored by Medtronic: MINIMED™ 780G System: Improving Clinical Outcomes, HCPs' and Users' Experience**

Amir Tirosh
Sheba Medical Center and Tel-Aviv University, Israel

09:40 **Sponsored by AstraZeneca: A New Era for the Management of Hyperkalaemia with New Potassium Binders**

David Wheeler
Centre for Nephrology, University College London, UK

10:00 **Sponsored by Novonordisk: Weight Loss Maintenance as a Therapeutic Target**

Gabriella Lieberman
Israel

10:20 **Sponsored by Eli Lilly: Known and Hidden in Anabolic Therapeutic Options in Israel and What can we do about it?**

Sophia Ish-Shalom
Elisha Hospital, Israel

10:40 **Sponsored by Pfizer: Acromegaly and Diabetes - A different Point of View**

Adnan Zina
Head of Endocrinology & Metabolism Department, Zvulon Medical Center, Clalit Health Services, Israel

11:00-12:30 Short Oral Presentations- Neuroendocrinology Hormones & Cancer

Chair: Merav Fraenkel

11:00 **GnRH Triggers Oscillation with Synchronised Spikes Contributing to Calcium Increase and Release of LH**

Yaron Cohen[1,2], Berta Levavi-Sivan[1], Michael Gutnick[2]
[1]*Animal Sciences, The Hebrew University of Jerusalem, Israel*
[2]*Koret School of Veterinary Medicine, The Hebrew University of Jerusalem, Israel*

11:10 **Gain-of-Function Variants in The Ubiquitin-Specific Protease 8 Gene (gof-USP8) Affect The Immune Microenvironment in Corticotroph-Derived Pituitary Adenomas (CPAs)**

Dahlia Greidinger[1,2], Ronit Mor-Cohen[1,3], Roni Zemet[1,3], Amit Tirosh[1,3]
[1]*Sackler Faculty of Medicine, Tel Aviv University, Israel*
[2]*Internal Medicine T, The Chaim Sheba Medical Center, Israel*
[3]*The Endocrine Oncology Bioinformatics Lab, Division of Endocrinology, Diabetes and Metabolism, the Chaim Sheba Medical Center, Israel*

11:20 **Adaptation of Colon Cancer Cells to the Brain Microenvironment: The Role of IRS2**

Inbal Greenberg[1,2], Anat Klein[1], Rachel Grossman[3], Ethan Sokol[4], Tami Rubinek[1,2], Ido Wolf[1,2]
[1]*Department of Oncology, Tel Aviv Sourasky Medical Center, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Israel*
[3]*Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Israel*
[4]*Foundation Medicine, Massachusetts Institute of Technology, USA*

11:30 **Q&A**

11:50 **Somatostatin Analogs (SSAs) Improve Respiratory Symptoms in Patients with Diffuse Idiopathic Neuroendocrine Cell Hyperplasia (DIPNECH)**

Taymeyah Al-Toubah[1], Jonathan Strosberg[1], Thor Halfdanarson[2], Kira Oleinikov[4], David J. Gross[4], Mintallah Haider[1], Mohamad Bassam Sonbol[3], Daniel Almquist[3], Simona Grozinsky-Glasberg[4]
[1]*Department of GI Oncology, H. Lee Moffitt Cancer Center and Research Institute, USA*
[2]*Department of Medical Oncology, Mayo Clinic Cancer Center Rochester, USA*
[3]*Department of Hematology and Oncology, Mayo Clinic Cancer Center Phoenix, USA*
[4]*Neuroendocrine Tumor Unit, ENETS Center of Excellence, Endocrinology & Metabolism Department, Hadassah-Hebrew University Medical Center, Israel*

12:00 **Long Term Outcome of Appendical Neuroendocrine Neoplasms**

Noa Rakover Klein[1], Haim Paran[2], Shmuel Avital[3], Vladimir Kravtsov[4], Rachel Chava Rosenblum[1], Pnina Rotman-Pikielny[1], Orit Twito[1]
[1]*Endocrine Unit, Meir Medical Center, Israel*
[2]*Surgery department A, Meir Medical Center, Israel*
[3]*Surgery Department B, Meir Medical Center, Israel*
[4]*Pathology Department, Meir Medical Center, Israel*

12:10 **Q&A**

11:00-12:30 Short Oral Presentations- Reproduction

Chair: Eran Gershon

11:00 **Immune Challenges in Early Life Alter Hypothalamic and Ovarian Function in the Adult Female**

Ben Bar-Sade[1], Or Eden[1], Reinhard Stoger[2], Gillian Bentley[3], Philippa Melamed[1]
[1]*Faculty of Biology, Technion-Israel Institute of Technology, Israel*
[2]*School of Biosciences, University of Nottingham, UK*
[3]*Department of Anthropology, Durham University, UK*

11:10 **A Novel Enhancer Regulates *Lhb* Transcription Utilizing DNA Structures to Drive Bi-directional eRNAs**

Tal Refael, Lilach Pnueli, Philippa Melamed
Faculty of Biology, Technion-Israel Institute of Technology, Israel

11:20 **Inducible Inhibition of Cripto Specifically in Trophoblast Cells at days Post Implantation Leads to Reduce Blood Supply to the Embryo**

Eran Gershon[1], Michal Elbaz[1], Ron Hadas[2], Evan Booker[3], Peter Gray[3]
[1]*Department of Ruminant Science, Agricultural Research Organization, Israel*
[2]*Biological Regulation, Weizmann Institute, Israel*
[3]*Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, USA*

11:30 **Vasorin Involvement in Ovarian Angiogenesis**

Dafna Ketter-Ratzon[1], Nitzan Rimon[1], Filip Bochner[2], Michal Neeman[1], Nava Dekel[1]
[1]*Biological Regulation, Weizmann Institute of Science, Israel*
[2]*Biomedical Engineering, ETH-University of science and Technology, Switzerland*

11:40 **Q&A**

12:00 **Fetal Anogenital Distance is Longer in Polycystic Ovary Syndrome Mothers**

Yoel Toledano[2], Sharon Perlman[1,3], Nufar Halevy[1], Zvi Kivilevitch[1], Yinon Gilboa[1,3]
[1]*Prenatal Ultrasound Unit, the Helen Schneider Women's Hospital, Rabin Medical Center, Israel*
[2]*Maternal Fetal Unit, the Helen Schneider Women's Hospital, Rabin Medical Center, Israel*
[3]*Sackler School of Medicine, Tel-Aviv University, Israel*

12:10 **Low Dose Cyproterone Acetate for the Treatment of Transgender Women – A Retrospective Study**

Naomi Even-Zohar[1], Yael Sofer[1], Iris Yaish[1], Merav Serebro[1], Karen Tordjman[1,2], Yona Greenman[1,2]
[1]*Institute of Endocrinology, Metabolism, Diabetes and Hypertension, Tel Aviv-Sourasky Medical Center, Israel*
[2]*Sackler Faculty of Medicine,, Tel Aviv University, Israel*

12:20 **Q&A**

11:00-12:30 Short Oral Presentations- Diabetes 2

Chair: Noga Minsky

11:00 **Gestational Diabetes Mellitus and Progression to Diabetes in Different Ethnic Groups in Israeli Population**

Meir Frankel, Noa Tsur, Anat Tsur
Endocrinology & Diabetes Clinic, Clalit Health Institute, Israel

11:10 **Relationship between Self-care and Cognition in Older People with Type 2 Diabetes**

Naama Peltz-Sinvani[1], Nadia Mordenfeld[1,2], Noa Gayus[1], Michal Azmon[1,3], Omri Guri-Twito[1], Tal Yahalom-Peri[1], Rachel Natovich[4], Tali Cukierman-Yaffe[1,2]
[1]*The Center for Successful Aging with Diabetes, Endocrinology Institute, Sheba Medical Center, Israel*
[2]*The Epidemiology Department, Sackler School of Medicine, Tel-Aviv University, Israel*
[3]*The Physiotherapy Department, Faculty of Health Sciences, Ariel University, Israel*
[4]*The Rehabilitation Hospital, Sheba Medical Center, Israel*

11:20 **Q&A**

11:35 **Prurigo Pigmentosa - An Acute Complication of Ketogenic Diet**

Neriya Levran[1,2,4], KinereT Mazor-Aronovitch[1,4], Shoshana Greenberger[1], Noa Levek[1,4], Bruria Sher[1], Elinor Mauda[1], Zohar Landau[3], Efrat Monsonego-Ornan[2], Orit Pinhas-Hamiel[1,4]
[1]*Pediatric Endocrine and Diabetes Unit, Sheba Medical Center, Edmond and Lilly Safra Children's Hospital, Ramat-Gan, Israel, Israel*
[2]*Robert H Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, P.O.B 12, 76100, Rehovot, Israel, Israel*
[3]*Pediatric Division,, Barzilai Medical Center, Ashkelon, Israel, Israel*
[4]*Juvenile Diabetes Center,, Maccabi Raanana, Israel*

11:45 **Virtual Clinic to Improve Type 1 Diabetes Control**

Noga Minsky[1], Liat Arnon[1], Nicole Morozov[2], Galia Zacay[2], Yulia Tsarbaev[1], Maya Laron-Hirsh[1], Hadar Miloh-Raz[1], Amir Tirosh[1]
[1]*Institute of Endocrinology, Sheba Medical Center, Tel-Hashomer, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

11:55 **The ADVICE4U STUDY: Opportunity to Optimize Insulin Pump Settings in Children, ADOLESCENTS and Young Adults with Type 1 Diabetes using Automated Artificial Intelligence System**

Revital Nimri[1], Tadej Battelino[2], Lori Laffel[3], Robert Slover[4], Desmond Schatz[5], Stuart Weinzimer[6], Klemen Dovc[2], Thomas Danne[7], Moshe Phillip[1]
[1]*Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Childrens Medical Center of Israel, Israel*
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12:05 Q&A

12:30-13:25 Poster Session

All-cause Mortality among Patients with Von Hippel-Lindau Disease and Pancreatic Neuroendocrine Tumors

Amit Tirosh[1,2], Liat Arnon[1]
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[2]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

Sex-dependant Response to Circadian Disruption in Diurnal Sand Rats

Carmel Bilu[1,2], Noga Kronfeld-Schor[6], Paul Zimmet[5], Vicktoria Vishnevskia-Dai[3], Haim Einat[4]
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The Quantitative Relationship between Autonomous Cortisol Secretion, Dysglycemia and the Metabolic Syndrome

Jonathan Bleier[1], Gadi Shlomai[1,2,4], Boris Fishman[1,4], Zohar Dotan[3,4], Barak Rosenzweig[3,4], Amir Tirosh[2,4]
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Difficulties in Utilization of Improved Glucose Monitoring in Type 1 Diabetics

Yehudit Carroll, Osnat Sidi-Wolf, Yosef Arad, Inna Katz, Inna Mechnik
Diabetes Clinic, Meuhedet, Israel

Biomarkers of Acute Kidney Injury in Diabetic Patients Treated with SGLT2 Inhibitors

Said Darawshi[1,2], Hiba Yaseen[2], Yori Gorelik[1,2], Caroline Faor[1,2], Aurian Szalet[3], Zaid Abassi[4], Samuel Heyman[3], Mogher Khamaisi[1,2]
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Course of Puberty and Growth Spurt in Boys with Type 1 Diabetes

Hana Shpitzer[1,2], Liora Lazar[1,2], Shlomit Shalitin[1,2], Moshe Phillip[1,2], Liat de Vries[1,2]
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BMI and Mortality in Surgical Patients – Is Higher Better?

Idit Dotan[1], Tzipora Shochat[2], Ilan Shimon[1,3], Amit Akirov[1,3]
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Adrenocortical Carcinoma – A Tertiary Center`s Recent 5-year Experience

Michal Ehrenwald[1], Karen Tordjman[1], Naftali Stern[1], Joseph Klausner[2], Ido Nachmany[2], Guy Lahat[2], Nir Lubezky[2], Yaakov Goykhman[2], Ido Wolf[3], Ravit Geva[3], Asaf Aizic[4], Sophie Barnes[5], Yona Greenman[1], Ester Osher[1]
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Inferior Petrosal Sinus Sampling – 16 Years of Experience from A Single Tertiary Center in Israel

Matan Fischer[1], Benjamin Glaser[1], Gil Leibowitz[1], David Gross[1], Joshua Stokar[1], Rivka Dresner-Pollak[1], José E. Cohen[2], J. Moshe Gomori[3]
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Characteristics of Hypothyroid Patients Achieving Long Term Euthyroidism on Levothyroxine Treatment

Merav Fraenkel[1], Jiaana Murad[2], Liad Alfandri[3], Victor Novack[2], Howard Tandter[4]
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Zebrafish GnRH Neurons Communicate Synaptically to Control the Assembly of the Circuit

Matan Golan[1,4], Jonathan Boulanger-Weill[3], Pierre Fontanaud[4], Anthony Pinot[4], Agnes Martin[4], Patrice Mollard[4], Lian Hollander-Cohen[2]
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Positive Modulation of SSTR2 Expression in a Neuroendocrine Tumor Model - Aiming towards Improving the Efficacy of Somatostatin Analogues Therapy

Ruba Simaan, Shani Avniel-Polak, David J. Gross, Simona Grozinsky-Glasberg
Neuroendocrine Tumor Unit, ENETS Center of Excellence, Endocrinology & Metabolism Department, Hadassah-Hebrew University Medical Center, Israel

Direct Oral Antucoagulants Decrease Bone Formation in MC3T3-E1 Cells

Irina Gurt[1], Sarit Hochberg-Klein[2], Einav Rosen[3], Rivka Dresner-Pollak[1]
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Plasma Hemoglobin Levels at Baseline and Follow-up as a Prognostic Marker for Progression and Mortality in Patients with Pancreatic Neuroendocrine Tumors (PNET)

Reut Halperin[1,2], Genya Aharon-Hananel[2,6], Muhamad Badarna[2], Dahlia Greidinger[3], Inbal Uri[2,4,5,6], Ruth Percik[2,4,5,6], Amit Tirosh[2,5,6]
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CB1 Receptor Regulates Renal GLUT2 Expression and Function via mTORC1 Signaling Pathway

Liad Hinden[1], Majdoleen Ahmad[1], Sharleen Hamad[1], Gergő Szanda[2], Aviram Kogot-Levin[3], Gil Leibowitz[3], Bernard Thorens[4], Joseph Tam[1]
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Gender Differences in the Presentation, Course and Outcomes of Primary Hyperparathyroidism

Tal Dadon[1], Sigal Levy[3], Gloria Tsvetov[1,2], Dania Hirsch[1,2]
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Distinct Prognostic Factors in Sporadic and Multiple Endocrine Neoplasia Type 1 (MEN1)-Related Pancreatic Neuroendocrine Tumors

Sapir Kon Kfir[1,7], Ruth Percik[2,3,7], Naama Halpern[4,7], Gadi Shlomai[1,3,7], Ido Laish[5,7], Amit Tirosh[3,6,7]
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Falling Insulin Requirements in Women with Pregestational Diabetes

Adi Carmi[1], Tali Hovav Shapiro[2], Yifat Wiener[2,4], Shlomit Koren[3,4], Ronit Koren[1,2,4]
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Reversibility of Type 1 Diabetes Mellitus. Myth or reality? A proof- of concept

Shmuel Levit[1,2], Naum Torban[1], Ifat Korek Abadi[3], Royi Barnea[3], Ildar N. Musin[2], Vyacheslav Levit[5], Chen Hanna Ryder[4]
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Endothelial Vascular Adrenal Cyst with Unusual Presentation

Gabriel Lichewitz[1], Marina Pal[2], Haggi Mazeh[3]
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Fatty Acid Binding Protein 4 (FABP4) Secreted From Visceral Adipose Tissue and Glucose Production in Gestational Diabetes Mellitus (GDM)

Ragad Madah[1,3], Idit Ron[1], Moran Rathaus[1], Benny Brandt[2,3], Roni Zemet[2], Shali Mazaki- Tovi[2,3], Amir Tirosh[1,3]
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Characteristics and Long –Term Outcomes of Patients Hospitalized for Diabetic Ketoacidosis

Michal Michaelis[1,2], Tzippy Shochat[3], Ilan Shimon[2,4], Amit Akirov[2,4,5]
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Somatostatin Not Only Inhibits GH, But Also Affects LH and FSH Secretion in Tilapia

Naama Mizrahi, Lian Hollander, Berta Levavi Sivan
The Robert H. Smith Faculty of Agriculture, Food and Environment., The Hebrew University in Jerusalem., Israel

Prevalence of Impulse Control Disorders in Patients with Pituitary Adenomas Treated with Dopamine Agonists

A Nathan, E Itzhakov, R Eldor, M Serebro, I Yaish, Y Greenman, K Tordjman
Institute of Endocrinology, Diabetes, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Israel

Carotenoids and Polyphenols Improve Bone Health Parameters in Human Osteoclasts, Osteoblasts and in a 3D Model of Bone

Alaa Nimer, Hilla Ovadia, Yoav Sharoni
Clinical Biochemistry and Pharmacology, Ben-Gurion University, Israel

Phaeochromocytoma-Paraganglioma (PPGL): Post-Operative Hypotension is a vanishing Phenomenon

Esther Osher[1], *Karen Tordjman[1], Joseph Klausner[2], Ido Nachmany[2], Boaz Sagie[2], Naftali Stern[1], Naomi Even Zohar[1], Guy Lahat[2], Ido Wolf[3], Lilach Zac[5], Sorina Otrimski[5], Asaf Aizic[6], Sophi Barnes[4], Yona Greenman[1]
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Low risk for all-cause Mortality among Patients with Lung Neuroendocrine Tumor Co-diagnosed with Pituitary Adenomas

Naama Peltz Sinvani[1,2], Ruth Percik[1,2], Inbal Uri[1,2], Sapir Kon Kfir[2,3], Amir Tirosh[1,2], Amit Tirosh[1,2]
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Blood Pressure Dynamics after Pubertal Suppression with Gonadotropin Releasing Hormone Analogs Followed by Testosterone Treatment in Transgender Male Adolescents

Liat Perl[1], Anat Segev-Becker[1], Galit Israeli[1], Erella Elkon-Tamir[1,2], Asaf Oren[1,2]
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Adipocyte Connexin-43 as a Mediator of Adipose Tissue Dysfunction in Obesity

Sophie T Ron[1,2], Idit Ron[1], Moran Rathaus[1], Rinat Livne[1], Nissim Oz[1], Assaf Rudich[3], Amir Tirosh[1,2]
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The Prevalence of Anti-Parietal Cell and Tissue-Transglutaminase Antibodies in Patients with Autoimmune Thyroid Disease

Rachel Chava Rosenblum[1], Reut Sapir[2], Menachem Shapiro[1,2], Sigal Levy[3], Pnina Rotman-Pikielny[1,2], Orit Twito[1,2]
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Efficacy of Pamidronate in The Treatment of Parathyroid Hormone-Related Hypercalcemia: A Real-World Study

Rachel Chava Rosenblum[1,2], Orit Twito[1,2], Liat Barzilay-Yoseph[1,2], Erez Ramaty[1], Noa Klein[1,2], Pnina Rotman-Pikielny[1,2]
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The OsteoSee System Measurements, Based On parametric Electrical Impedance Tomography (pEIT), Correlate with Dual X-Ray Absorptiometry Results for the Diagnosis of Osteoporosis

Vanessa Rouach[1,2,3], Yuliana Pushevsky, Yuliana Pushevsky[2], Alla Mayboroda[2], Alina Osherov[2], Michal Guindy[2]
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Long-term Response to Cabergoline Treatment in Men with Macroprolactinoma is Independent of Tumor Size

Yaron Rudman[1,3], Hadar Duskin-Bitan[1], Barak Pertzov[2], Yossi Manisterski[1], Hiba Masri-Iraqi[1], Ilan Shimon[1]
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The Challenges of Treating Glucokinase MODY During Pregnancy

Tal Schiller[1], Oren Barak[2], Yael Vinter[2], Elena Kirzhner[1], Viviana Ostrovsky[1], Hilla Knobler[1], Taiba Zornitzki[1]
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Insulin Requirement through-out Pregnancy in Women with Type 1 Diabetes

Roy Shalit[1], Nimrod Dori-Dayan[2], Ohad Cohen[1,3], Noga Minsky[1], Roni Zemet[2], Rakefet Yoeli-Ullman[2], Shali Mazaki-Tovi[2,3], Tali Cukierman-Yaffe[1,3]
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Gestational Weight Gain does-not Affect Insulin Requirement During Pregnancy in Women with Type 1 Diabetes

Roy Shalit[1], Nimrod Dori-Dayan[2], Roni Zemet[2], Ohad Cohen[1,3], Noga Minsky[1], Shali Mazaki-Tovi[2,3], Rakefet Yoeli-Ullman[2], Tali Cukierman-Yaffe[1,3]
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Unannounced Meal Challenges in a Protected Free-Living Environment using the Medtronic Advanced Hybrid Closed Loop System

Roy Shalit[1], Maya Laron Hirsh[1], Ohad Cohen[1,2], Natalie Kurtz[2], Roy Anirban[2], Benyamin Grosman[2], Amir Tirosh[1]
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OsteOosee: A Novel Tabletop Device for Screening and Diagnosing Osteoporosis

Liana Tripto-Shkolnik[2], Ido Tilbor[1]
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Predicting BMD Result: Validation of Osteoporosis Risk Indices in Israeli Population

Ido Tilbor[2,3], Iris Vered[1,3], Liana Tripto-Shkolnik[1,3]
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Long-term follow up of Denosumab Discontinuers with Multiple Vertebral Fractures in the Real World

Liana Tripto-Shkolnik[1,2], Naama Yekutiel[3], Gabriel Chodick[2,3], Varda Shalev[2,3], Inbal Goldshtein[3]
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The Impact of Flash Glucose Monitoring Technology on Glycemic Control and Healthcare Services Consumption in Patients with Type 1 Diabetes - A Nationwide Cohort Study

Anat Tsur[1], Rena Pollack[2], Avivit Cahn[2], Meirav Israel[3], Ilan Feldhamer[4], Ariel Hamerman[5]
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Denosumab-induced Hypocalcemia: Does Gender Play a Role?

Talia Diker-Cohen[2,3,6], Oren Amitai[3,5], Tzippy Shochat[2,4], Ilan Shimon[2,3], Gloria Tsvetov[1,2,3]
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Temporal Trends in Incidence, Evaluation and Management of Neuroendocrine Neoplasms of the Appendix- 14 Years` Experience

Orit Twito[1,5], Haim Paran[2,5], Shmuel Avital[3,5], Vladimir Kravtsov[4,5], Rachel Chava Rosenblum[1,5], Pnina Rotman-Pikielny[1,5], Noa Klein[1,5]
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Atypical Femoral Fractures and Bisphosphonates Exposure among Patients Participating in a Fracture Liaison Service

Noa Israeli[5], Merav Fraenkel[1,5], Roni Gat[3,5], Viktoria Makarov[2,5], Dayana Cohen[1,5], Vitaly Medvedovsky[1,5], Lior Baraf[1,5], Tamar Eshkoli[1,5], Victor Novack[3,4,5], Uri Yoel[1,5]
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Sodium Glucose Cotransporter 2 Inhibitors in Acromegalic Patients with Diabetes
Adnan Zaina[1], Ilan Shimon[2], Yuval Grober[3], Ali Abid[1], Eldad Arad[1], Elena Golden[1]
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[3]*Division of Neurosurgery, Galilee Medical Center, Bar- Ilan university, the Azrieli Faculty of Medicine, Safed., Israel*

Subacute Thyroiditis: Clinical Presentation and Long-term Follow-up
Taiba Zornitzki[1], Sorcha Mildiner[2], Tal Schiller[1], Viviana Ostrovsky[1], Hilla Knobler[1]
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13:25-13:45 Industry Session 2

13:25 **Sponsored by Pfizer: Vaccines in the COVID-19 era: What is the Role of Pneumococcal Vaccines in Patients with Diabetes?**
Yoel Toledano

13:45-14:00 Break - Visit the Exhibition

14:00-15:30 Symposium 4- Pediatric Endocrinology

Chair: David Zangan

14:00 **Gonad Determination and Differentiation**
Anu Bashamboo, *Paris, Paris, France*

14:30 **Part 1 - How to Raise: The Road Not Taken, Three Challenging Cases**
Anat Segev-Becker
Dana-Dwek Children Hospital, Tel Aviv, Pediatric Endocrinology and Diabetes Unit, Israel

14:45 **Part 2: How to raise: The Road Not Taken, Two Challenging Cases**
Tal Ben Ari
Pediatric Endocrinology and Diabetes Unit, Wolfson Medical Center, Holon, Israel

15:00 **Q&A**

15:30-16:30 IES Prize Session

Chovers Prize: Dr. Michal Silber
Lindner Prize: **Dr. Limor Landsman**

16:30-18:00 Symposium 5- Endocrine and Developmental Functions of Long Non-Coding RNA

Chair: Philippa Melamed

16:30 **Functions of Long Noncoding RNAs in Early Development and Regeneration**
Igor Ulitsky
The Weizmann Institute of Science, Rehovot, Israel

16:55 **Membrane Receptor for Thyroid Hormones in Cancer: Role in Gene Transcription**
Osnat Ashur-Fabian
Sackler School of Medicine, Tel-Aviv University, Israel

17:20 Regulation of Pancreatic Endocrine Cell Differentiation by Long Noncoding RNAs
Lori Sussel
University of Colorado, Colorado Denver, USA

17:45 Panel Discussion and Q&A

18:00-18:15 Break - Visit the Exhibition

18:15-19:45 Symposium 6- Bone Fragility: Update on Risk Factors, Diagnosis and Therapy

Chair: Liana Tripto-Shkolnik

18:15 Automated Opportunistic Osteoporotic Fracture Risk Assessment using Computed Tomography Scans to Aid in FRAX Underutilization
Eldad Elnekave
Department of Radiology, Rabin Medical Center, Israel
Chief Medical Officer, Zebra Medical Vision, Israel

18:40 Skeletal Fragility in Diabetes, a Serious and Under-Diagnosed Complication
Rivka Dresner Pollak
Hadassah Medical Center, Jerusalem, Israel

19:05 New Insights into Anabolic Therapy for Osteoporosis
Michael McClung
Oregon Osteoporosis Center, Portland, USA

19:30 Panel Discussion and Q&A

19:45-20:55 Plenary Lecture 4

Chair: Ruth Shalgi

19:45 CRISPR based Technology as a Potential Therapeutic to Treat Severe Obesity
Nadav Achituv
Institute for Human Genetic, Uc San Francisco, USA

20:25 Q&A

20:40 Closing Remarks
Gil Leibowitz Lev

ABSTRACTS


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Symptomatic and Asymptomatic Hypoglycemia Post Three Different Bariatric Procedures: A Common and Severe Complication

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Background: The prevalence of post-bariatric surgery hypoglycemia (PBH) remains unclear due to diagnostic criteria variability,
types of bariatric procedures and possible unawareness.

Objective: To determine the frequency, pattern and severity of symptomatic and asymptomatic hypoglycemia in subjects post three different bariatric procedures performed 1 year before evaluation and a group of obese subjects before surgery.

Design and Setting: Observational cohort study. Fifty-one consecutive patients participated: post Roux-en-Y gastric-bypass (RYGB) (n=16), post omega-loop gastric-bypass (OLGB) (n=12), post sleeve-gastrectomy (SG) (n=15), obese subjects before surgery (controls) (n=8). Hypoglycemic events (glucose ≤54 mg/dL) and severe hypoglycemia (glucose ≤40 mg/dL) were evaluated by symptoms` questionnaire, mixed-meal tolerance test (MMTT) and continuous glucose monitoring (CGM).

Results: According to questionnaires, meal-related complaints were reported in 11 (26%) of the surgical group and in one control subject. During MMTT, 88%, 82% and 67% experienced hypoglycemia in RYGB, OMGB and SG groups, respectively, vs. none of the controls (P0.001). Severe hypoglycemia occurred in 38%, 45% and 7% in RYGB, OMGB and SG groups, respectively (P=0.025), but only 10 of the total operated patients (24%) reported any symptoms. During CGM, fasting hypoglycemic events occurred more in RYGB and OLGB vs. SG group: 55%, 63% and 17% respectively (P=0.036).

Conclusions: PBH is very common after RYGB, OMGB and SG and can be severe especially following bypass procedures. Our results show that hypoglycemia occurs not only postprandially but also in the fasting state, especially following bypass procedures. In most cases, there were no specific complaints, possibly leading to its underestimation

GnRH Triggers Oscillation with Synchronised Spikes Contributing to Calcium Increase and Release of LH

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In vertebrates, reproduction is regulated by the hormones of the hypothalamus–pituitary–gonad axis. Luteinizing hormone (LH) is released from pituitary gonadotrophs in a distinctive periodic pattern; the mechanisms underlying this pulsatile release are not well understood. In mammals, LH and FSH are colocalized in the same cell. In fish, by contrast, the hormones are produced and released from distinct cell types; this allows us to study the mechanism of LH release independently. We have created a transgenic fish with GFP and the calcium marker RCaMP in LH cells. Double patch clamp recordings in a pituitary slice preparation reveal that LH cells comprise an electronically coupled syncytium. Brief exposure to GnRH triggers a prolonged, slow, 0.5 Hz oscillation; this is the optimal frequency for synchronization of the cells. Bursts of TTX-sensitive action potentials are generated on the depolarizing peaks of the oscillation. Ca imaging reveals that a two second exposure to GnRH triggers prolonged (10 min) Ca increase in all LH cells, followed by a longer refractory period. Exposure to TTX attenuates the Ca increase and LH release. Suggesting that sodium action potentials generated during the GnRH-induced oscillation cause entry of Ca as part of the releasing process. We propose that these electrical and imaging responses following brief GnRH exposure reflect the mechanisms that underlie pulsatile LH release.

Burosumab Therapy in Children and Adolescents with X-linked Hypophosphatemia: The Real-life Israeli Experience

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Background: X-Linked Hypophosphatemia (XLH) is an inherited disease caused by mutations in the PHEX gene, resulting in elevated FGF23 concentrations which lead to hyperphosphaturia and decreased synthesis of 1,25-dihydroxy-vitamin D. Patients with XLH suffer from hypophosphatemia, rickets, short stature and significant morbidity, previously treated (with partial success) with multiple daily doses of oral phosphate salts and active vitamin D. Burosumab, a human monoclonal antibody against FGF23, is a novel treatment for XLH introduced in Israel in 2017. We describe the Israeli experience with this agent.

Methods: Real-life data of children with XLH followed at seven medical centers were collected from diagnosis through burosumab treatment. Outcome measures: anthropometric measurements, laboratory parameters, imaging and adverse events were retrieved from the medical charts. Skeletal changes were evaluated by radiography using the rickets-severity scale (RSS) and the radiographic global impression of change (RGI-C).

Results: Twenty-six patients with XLH (age 3-16 years) received burosumab subcutaneously every 2 weeks for 9-20 months. The initial dose was 0.4-0.8 mg/kg, titrated by serum phosphate according to recommendations. Phosphate homeostasis improved in all patients as evidenced by increased renal tubular reabsorption of phosphate, normalization of phosphate and alkaline phosphatase levels and increased 1,25-dihydroxy-vitamin D. Rickets severity score decreased and linear growth increased in most patients. No severe adverse events were reported.

Conclusions: Burosumab had a favorable effect on renal tubular reabsorption of phosphate and rickets score in patients treated under real-life circumstances. Further surveillance is needed to evaluate long-term effects on bone health and adult height.

*equal contribution

Low Dose Cyproterone Acetate for the Treatment of Transgender Women – A Retrospective Study

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Introduction: Transgender women with intact gonads receive lifelong hormonal treatment in order to suppress physiologic androgen production. Cyproterone acetate (CA) is the most prevalent antiandrogenic drug prescribed for this indication in Europe, with a dose range between 25-100 mg/day.

Aim: To assess the effectiveness and safety of low dose (50 mg/day) CA treatment.

Methods: Historical cohort study of transgender women treated in our department between January 2000 and October 2018.

Results: There were 42 transgender women in the low dose group (LDG) and 32 in the high dose group (HDG). Age (27.9 ± 1.6 vs.28.9 ± 1.7 years) and follow up time (16.2 ± 2.2 vs. 20.1 ± 2.1 months) were similar in the LDG and HDG, respectively. At the last available visit, testosterone levels were effectively and similarly suppressed in both treatment groups (0.6 ± 0.1 vs 0.8 ± 0.3 nmol/l; p=0.37, for LDG and HDG respectively). Prolactin (659 ± 64 vs 486 ± 42 mIU/ml, p=0.02), LDL cholesterol (96.1 ± 5 vs 78.5 ± 4 mg/dl, p= 0.02) and triglycerides (93.3 ± 9 vs 69 ± 5 mg/dl; p=0.02) were higher in the HDG compared with LDG respectively. Side effects were common in the HDG (four cases of increased liver enzymes, one case of pulmonary embolism, sudden death, and suicide attempt).

Conclusion: We show for the first time that anti-androgenic treatment of transgender women with low dose CA is as effective as high dose treatment, but safer. We suggest the incorporation of this observation in future guidelines.

Somatostatin Analogs (SSAs) Improve Respiratory Symptoms in Patients with Diffuse Idiopathic Neuroendocrine Cell Hyperplasia (DIPNECH)

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Introduction: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare lung disease associated with proliferation of neuroendocrine cells in the lung and multifocal neuroendocrine tumorlets/tumors. Although usually considered an indolent condition, DIPNECH causes chronic, progressive cough and dyspnea which can adversely impact quality of life. There is very limited information on the treatment of this condition.

Aims: To assess changes in symptoms as well as pulmonary function tests (PFTs) in response to somatostatin analogues (SSAs) treatment.

Methods: Patients with clinical and/or pathological diagnosis of DIPNECH and chronic respiratory symptoms were treated with SSAs at the Moffitt Cancer Center, Hadassah Medical Center, and Mayo Clinic. Their charts were reviewed to assess changes in symptoms and pulmonary function tests.

Results: 42 patients were identified who had either chronic cough or dyspnea due to proven or suspected DIPNECH and who had received treatment with an SSA. 33 patients experienced symptomatic improvement. Additionally, 14 out of 15 patients in whom pulmonary function tests (PFTs) were checked were noted to have an improvement in FEV1 following treatment.

Conclusions: SSAs treatment can improve chronic respiratory symptoms and PFTs in patients with DIPNECH.

Relationship between Self-care and Cognition in Older People with Type 2 Diabetes

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Introduction: Self-care is a cornerstone in diabetes management. People with lower cognitive function have worse self-care abilities. Less is known regarding the cognitive domains and the self-care capacities indices that are most effected.

Objective: To delineate the association between scores on several cognitive assessment tools and self-care capacity indices in older people with type-2 diabetes.

Methods: A cross-sectional study conducted amongst individuals with diabetes 60Y. The association between several self-care capacity indices [the Summary of Diabetes Self-Care Activities Assessment (SDSCA) questionnaire, severe hypoglycemia, Physical Activity Questionnaire (PAQ)] and different cognitive assessment tools was assessed using linear/logistic regression.

Results: This analysis pertains to the first 122 consecutive participants that were assessed at the Center for Successful Aging with diabetes. 64.8% were men; mean age 70.4±6.2 years.

Higher A1C values were associated with lower Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution (DSST) cognitive score (P=0.016; 0.03 respectively). Lower scores on the Physical Activity Questionnaire (PAQ) and reporting of a severe hypoglycemia episode were also associated with lower MOCA scores (P= 0.017 and 0.009, respectively). Lower scores on the SDSCA exercise, blood-glucose testing and medication domains were associated with lower NeuroTrax Global Cognitive Score (GCS) (P=0.023, 0.014, 0.029 respectively). A similar trend was seen for the NeuroTrax domain specific scores (executive function, memory, processing speed).

Discussion: In older people with type-2 diabetes worse self-care capacity abilities are associated with lower cognitive test scores in several domains. Larger studies with long term follow-up are needed in order to further validate these results.

Virtual Clinic to Improve Type 1 Diabetes Control

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A multidisciplinary virtual T1D clinic was launched at Sheba Medical Center to improve access to care and diabetes outcomes across Israel as measured by HbA1c and ambulatory glucose profile (AGP). The service overcomes time and geographic constrains by providing care remotely between annual visits. We report our experience with our first 32 adult T1D patients (56% female) over an average of 6 months. Thirteen patients (41%) joined the clinic from Israel's Northern District and the remainder were from central Israel. At baseline, mean patient age was 38±16, with a mean duration of diabetes of 13±8 years. Most patients (88%) managed their T1D using CGM augmented pump therapy, with 6% using insulin pumps with SMBG and additional 6% using multiple daily insulin injections with CGM. Baseline HbA1c was 7.7±1.1%, and 22% had documented diabetes related complications. After 3 months there was a mean HbA1c reduction of 0.4% (n=19,p=0.007). During this period average CGM glucose improved from a baseline of 173±36mg/dl to 160±21 mg/dl (n=15,p=0.036). There was a non-significant trend toward improvements in time in range (TIR) (70-180mg/dl) from 55±20% to 57%±18%. Following 6 months of intervention, mean glucose was significantly improved compared to baseline, at 154±25mg/dl (n=14,p=0.01) and there was a stronger trend toward improved TIR: 64±16% (p=0.05). Time in clinically significant hypoglycemia (54mg/dL) did not change significantly over the 6 month period (1.4 to 2%,p=0.35). In conclusion, this virtual T1D clinic has provided care to patients across Israel remotely and conveniently, leading to significant improvements in HbA1c and AGP measures.

Cushing's Syndrome (CS) in the 21st Century, Not What it Used to Be: A Single Institution Experience

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Background: Solid clinical suspicion should always precede any investigation for a rare diagnosis of CS. However, the current obesity epidemic has obscured the discrimination between subjects "at true risk" for CS from those with the metabolic syndrome.

Aim and Design: To characterize the clinical presentation of modern era CS at Tel Aviv Sourasky Medical Center in a retrospective study of confirmed CS patients diagnosed between 2000-2018.

Results: The CS incidence rose steadily over the years. 76 patients were identified with CS (79% women): 49 Cushing's disease (64.5%), 16 benign adrenal process (21.1%), 7 ACC (9.2%), and 4 cases of ectopic ACTH secretion (5.3%). A clinical suspicion of CS was the reason for the diagnostic workup in only 15 subjects (19.7%). Half of the time, absence of typical CS appearance was emphasized. Common co-morbidities were hypertension (62.7%), hyperlipidemia (48.6%), obesity (48.6%), osteoporosis (38.4%), and diabetes (36.8%). In both genders, muscle weakness was the most common symptom (29.6%). Weight gain was reported by only 17.1% of subjects. Abdominal obesity was present in 70%, but typical striae in only 20.8% of subjects, lower than quoted in the literature. A composite disease severity score correlated with serum cortisol after overnignt 1 mg dexamethasone test (r=0.42, p=0.003), but not with UFC.

Conclusions: From our single institution experience, the incidence of diagnosed CS appears to be rising. Regrettably, a majority of modern era CS patients defy diagnosis due to their atypical presentation. Our findings add further uncertainty as to which patients should be screened for CS.

Denosumab Associated Risk of Malignancy- systematic Review and Meta-analysis of Randomized Controlled Trials

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Context: Possible increased risk of malignancy in patients treated with denosumab has been apprehended due to inhibition of the immune modulator receptor activator of nuclear factor κ-B ligand.

Objective: To assess the risk of malignancy during denosumab treatment.

Data Sources: PubMed and Cochrane Central Register of Controlled Trials were searched up to May 27, 2019.

Study Selection: All randomized controlled trials of denosumab (60 mg every 6 months) versus any comparator. Trials with use of higher drug doses were excluded.

Data Extraction: Data were independently extracted by two reviewers. We used a fixed effect model to pool risk ratios (RR) with 95% confidence intervals (CI). Sensitivity analysis was based on risk of bias in allocation concealment.

Data Synthesis: Twenty-five trials (21,523 patients) were included. The risk of adverse events of malignancy was comparable between denosumab and other comparators (absolute risk difference 0%, RR 1.08 [95% CI, 0.93-1.24], I2=0%). Sensitivity analysis showed similar results. The risk of malignancy did not differ between groups in any of the subgroup analyses, including stratification by race, individual comparators, indications for treatment and in longer duration of drug exposure (≥24 months, 9 studies). The risk ratio of cancer-related death was comparable between groups.

Conclusions: Denosumab treatment at a dose of 60 mg every 6 months for up to 48 months is not associated with a higher incidence of neoplasms. Early concerns about a potential increased risk of malignancy resulting from an immunomodulatory effect of denosumab can probably be alleviated.

Macrophage JAK2 Deficiency Accelerates Atherosclerosis through Defects in Cholesterol Efflux

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Atherosclerosis is a chronic inflammatory condition whereby macrophages (Mϕ) play a major role. Janus Kinase (JAK)2 is pivotal in inflammatory and metabolic signaling, and $JAK2^{V617F}$ activating mutation with enhanced clonal hematopoiesis is implicated in atherosclerosis. However, the essential in vivo role of Mϕ (M)-JAK2 in atherosclerosis is unclear. To this end, we generated atherosclerosis-prone ApoE-null mice deficient in M-Jak2 using the cre-loxP system under LysM promoter (M-Jak2KO). These, along with M-Jak2 wildtype (WT) littermate controls were fed atherogenic diet for 16 weeks starting at six weeks of age. M-Jak2KO mice showed less weight gain and improved glucose and lipid homeostasis compared to controls. Surprisingly, M-Jak2KO mice exhibited increased plaque burden with larger necrotic core and higher Mϕ content within plaques in the lesser curvature. Clonogenic assay did not demonstrate increased clonal expansion of M-Jak2 bone marrow (BM). 3 and 24-hour bromodeoxyuridine (BrdU) incorporation into plaques showed no differences in Mϕ proliferation and recruitment, respectively. While cholesterol uptake in BM-derived Mϕ (BMDM) was similar, M-Jak2KO BMDM showed defective efflux both basally and after cAMP-mediated ATP-binding-cassette-A1 (ABCA1) induction. JAK2-inhibition with AG490 caused a similar reduction in efflux in WT, with no further reduction in the KO. Mϕ differentiated from peripheral blood monocytes (PBM) of healthy donors showed a similar decrease in efflux with AG490. Intriguingly, Mϕ differentiated from PBM of individuals with $JAK2^{V617F}$ mutation showed increased cholesterol efflux, which was reduced with AG490.

In conclusion, M-Jak2-deficiency leads to accelerated atherosclerosis despite improved systemic metabolic parameters through a functional defect in cholesterol efflux.

A Novel Enhancer Regulates *Lhb* Transcription Utilizing DNA Structures to Drive Bi-directional eRNAs

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Recent advances in high-throughput sequencing have revealed numerous non-coding RNAs (lncRNAs), some of which are transcribed from transcriptional enhancers (eRNAs). We have discovered a putative transcriptional enhancer of the gene encoding the luteinizing hormone β subunit (Lhb), which is transcribed into bi-directional enhancer RNAs (eRNAs). This region is enriched with H3K4me1 and is in physical contact with the proximal Lhb promoter. To confirm its function, we expressed CRISPR dCas9- KRAB/ VP64 in a gonadotrope cell line, with gRNA targeting the enhancer, which significantly altered Lhb mRNA levels. Moreover, we detected, using circular dichroism, unique DNA structures in this region, one of which is sensitive to changes in environmental conditions. These structures, a G-quadruplex and an I-motif, are often found in gene regulatory regions. While the G-quadruplex is known to repress transcription, the function of the I-motif was suggested to be stimulatory, although its function is not yet understood. We generated a gonadotrope cell line with the Lhb enhancer sequence linked to two reporter genes. Treatment of these cells with G-quadruplex stabilizing agent, Pyridostatin (PDS) reduced the expression of both genes. We found that the High Mobility Group Box 2 (HMGB2) binds at this Lhb enhancer region. HMGB2 binds DNA structures, and can increase DNA flexibility and looping to promote physical proximity between distant DNA regulatory regions. Knockdown of HMGB2 in gonadotropes significantly reduced Lhb and eRNA expression. We hypothesize that binding of HMGB2 to the G-quadruplex/I-motif enables transcription of both eRNA and Lhb by allowing DNA flexibility at the enhancer.

Fatty Acid-binding Protein 4 – A Key Regulator in Pathophysiology of Diabetic Ketoacidosis in Type 1 Diabetes

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Objective: Fatty acid-binding protein 4 (FABP4) is an adipokine with key regulatory role in glucose and lipid metabolism. We aimed to evaluate the role of FABP4 in the pathophysiology of diabetic ketoacidosis (DKA) in type 1 diabetes (T1D).

Methods: Clinical and laboratory data were prospectively collected from consecutive children presenting with new onset T1D. In addition to blood chemistry and gases, insulin, and C-peptide, serum FABP4 and free fatty acids were collected upon presentation and 48 hours after initiation of insulin treatment.

Results: Included were 33 children (mean age 9.3±3.5 years, 52% males) of whom 14 (42%) presented with DKA. Mean FABP4 level was higher in the DKA group compared to the non-DKA group (12.1±8.2 vs. 7.4±6.8ng/ml, p=0.004, respectively). FABP4 level directly correlated with HbA1c at presentation and inversely with venous pH and bicarbonate levels (p8.1±3.3 ng/ml and 4.5±3.9ng/ml in the DKA and non-DKA groups, respectively (p0.05). An FABP4 level of 7.22 ng/ml had a sensitivity of 86% and a specificity of 78% for the diagnosis of DKA, with an area under the ROC curve of 0.78 (95%CI 0.6-0.95, p=0.008). In a T1D mouse model, FABP4 knock-out mice exhibited a marked reduction in ketogenesis compared to wild-type controls (3.5-fold reduction, p0.05), despite a similar reduction in insulin levels and marked hyperglycemia.

Conclusions: Given the key regulatory role of FABP4 in glucose and lipid metabolism, circulating FABP4 is likely an important regulator of ketogenesis in type 1 diabetes.

The Relationship between Glucose Control & Cognitive Function in People with Diabetes after a Lacunar Stroke

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Background & Objective: Lacunar strokes and diabetes are risk factors for cognitive dysfunction. Thus elucidating modifiable risk factors has large public health implications. One such factor may be glycemic status, as measured by glycosylated hemoglobin (A1C). The aim of this study was to assess the relationship between A1C and cognitive function in people with diabetes after a lacunar stroke.

Methods: The effect of baseline and follow-up A1C on the baseline and the change in Cognitive Assessment Screening Instrument (CASI) over time among participants with a median of 2 cognitive assessments (range 1-5) was examined in of 942 individuals with diabetes and a lacunar stroke who participated in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial (ClinicalTrials.gov number, NCT00059306).

Results: Every 1 % higher baseline A1C was associated with a 0.06 lower standardized CASI z-score (95% CI -0.101, -0.018). Higher baseline A1C values were associated with lower CASI z-score over time (p for interaction=0.037). A 1% increase in A1C over time, corresponded with a CASI score decrease of 0.021 (95% CI -0.0043, -0.038) during follow-up. All these remained statistically significant after adjustment for age, sex, education, race, depression, hypertension, hyperlipidemia, BMI, CVD, OSA, diabetic retinopathy, nephropathy insulin use and White Matter Abnormalities.

Conclusion: This analysis of 942 individuals with diabetes after a lacunar stroke demonstrates a relationship between A1C and change in cognitive scores over time. Intervention studies are needed in order to delineate if better glucose control could slow the rate of cognitive decline in this high risk population.

Proximal Tubule mTORC1 Is a Central Player in the Pathophysiology of Diabetic Nephropathy and its Correction by SGLT2 Inhibitors

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Introduction: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) ameliorate diabetic nephropathy (DN), even in advanced disease. mTORC1 is a central nutrient sensor, which may promote cellular stress, inflammation, and fibrosis. Its role in DN is unclear.

Aim: Clarify mTORC1 role in the development of DN and therapeutic effects of SGLT2i.

Methods: Diabetic Akita mice were treated with dapagliflozin for 12-weeks. mTORC1 activity was analyzed by Western-blotting and immunofluorescence for phospho-S6; markers of tubular injury and fibrosis were evaluated. Cre-lox system was used for lineage-tracing renal proximal tubule cells (RPTCs) and generating RPTC-specific Tsc1 and Raptor knockout mice.

Results: Akita mice developed DN with albuminuria and decreased creatinine clearance. Lineage-traced RPTCs in Sglt2-Cre; Rosa26-YFP reporter mice showed that most mTORC1 activity is localized in RPTCs. Immunofluorescence and Western blotting showed that RPTC mTORC1 activity was increased in diabetic Akita mice; this was associated with increased tubular injury (Cystatin-C) and fibrosis (Collagen III). Dapagliflozin prevented mTORC1 activation, tubular injury, interstitial fibrosis and renal failure. Conditional activation of mTORC1 in RPTCs by knockout of Tsc1 mimicked DN, inducing fibrosis and renal failure, and abrogated the beneficial SGLT2i effects. Partial inhibition of mTORC1 by conditional deletion of Raptor in Akita RPTCs prevented fibrosis and decline in renal function.

Conclusion: RPTCs mTORC1 is a critical node that mediates the development of DN and the protective effects of SGLT2i, and as such, a most attractive therapeutic target.

Inducible Inhibition of Cripto Specifically in Trophoblast Cells at days Post Implantation Leads to Reduce Blood Supply to the Embryo

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During Embryo implantation, adhesion is immediately followed by uterine Angiogenesis.
Cripto is a Multifunctional Signaling factor that stimulates Angiogenesis.
Previously, we have demonstrated Cripto indispensably for Embryo implantation.
Herein, we aimed to explore the role of Cripto in placenta formation at early days of pregnancy.
Embryos were infected with Lentiviruses harboring a Doxycycline (DOX)-inducible Cripto Antagonist, ALK4-Fc, with Neptune and FLAG proteins as markers for inducible expression.
Those Embryos were return to Psudopregnant females that were given DOX in their drinking water or not on day E6.5, two days after implantation.
The Females were sacrificed at day E9.5 and implantation sites were counted and taken for Histological examination of placenta Angiogenesis.
Only Embryos exposed to DOX expressed Neptune and FLAG, indicating inducible expression of this proteins and thus ALK4-Fc.
Examination of implantation site immediately upon their removal from the uteri revealed normal Phenotype in 90% of implantation sites isolated from the non-treated females, as compared to 53% of pre-absorbed or absorbed implantation sites in uteri isolated from DOX-treated females.
Histological examination of those implantation sites revealed reduced blood supply to the Embryos in those implantation sites.
This was confirmed by injection of Dextran-Texas red i.v. into to the tail vain.
We further found reduction in Blood accumulation in implantation sites with inhibited Cripto as well as reduced and shallow Embryo invasion to the mother uterus.
Cripto inhibition at days E6.5-E9.5 of pregnancy results in shallow invasion of the embryo to the mother uterus and reduced Blood supply to the Embryo.

Reversal of Diet-induced Hepatic Steatosis by Peripheral CB1 Receptor Blockade is miRNA-22/SIRT1/PPARα Dependent

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Introduction: The endocannabinoid (eCB) system is increasingly recognized as being of crucial importance in obesity-related metabolic abnormalities, one of which is liver injury and hepatic steatosis.
eCBs, via activation of the cannabinoid-1 receptor (CB1R) in the liver, modulate Hepatic Lipid Metabolism. However, the underlying Molecular Mechanisms are largely unknown.

Aim: Elucidating the Molecular singling pathways by which CB1R contributes to fat accumulation in the Liver.

Methods: By using an Integrative approach of computational biology, High-throughput micro RNA Sequencing, Mouse Genetic, and Pharmacological Strategies we Identified a new signaling pathway by which hepatic CB1R Involves in the Development of fatty Liver Disease.

Results: Unbiased normalized phylogenetic profiling analysis revealed that CB1R evolutionarily coevolves with peroxisome proliferator-activated receptor-alpha (PPARα).
In diet-induced obese (DIO) mice, peripheral CB1R blockade (using AM6545) induced the reversal of hepatic steatosis and improved liver injury in WT, but not in PPARα-/- mice.
The antisteatotic effects, mediated by AM6545 in WT DIO mice, were accompanied by increased hepatic expression and activity of PPARα.
Moreover, AM6545 was unable to rescue hepatic steatosis in DIO mice lacking Liver sirtuin 1 (SIRT1), an upstream regulator of PPARα.
Both of these signalling molecules were modulated by CB1R, as measured in hepatocytes exposed to lipotoxic conditions or treated with CB1R agonism in the absence/presence of AM6545.
Furthermore, using microRNA transcriptomic profiling, we found that CB1R regulated the Hepatic expression of miR-22, which was further found to specifically target SIRT1 and PPARα.

Conclusions: Peripherally CB1R blockade induces antisteatotic effects by modulating the miR-22/SIRT1/PPARα signaling pathway.

Immune Challenges in Early Life Alter Hypothalamic and Ovarian Function in the Adult Female

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Environmental conditions in early life can affect a woman's subsequent reproductive function.
Using a Mouse model, in which young Females are given DSS to induce colitis, we found that Immunological stress in early life delays puberty onset, Decreases numbers of growing follicles and reduces numbers of atretic follicles in the ovaries.
We aimed to elucidate the mechanisms mediating this altered reproductive function. Srd5a1, which encodes the enzyme 5α-reductase-1, was down-regulated in ovaries of DSS-treated mice, indicated by RNA seq. This correlated with increased DNA methylation of a putative transcriptional enhancer.
Srd5a1 mRNA levels were also reduced in the ypothalamus, specifically in the arcuate Nucleus, as were levels of Gnrh and Kiss1.
5α-reductase-1 is responsible for the synthesis of Allopregnanolone, a Neuroactive steroid that is reported to affect GnRH secretion by modulating GABAA or NMDA receptors.
We found that the GABA Agonist Muscimol increased GnRH secretion but did not affect its mRNA levels in the GnRH Neuronal cell-line (GT1-7).
However, inhibiting 5α-reductase-1 decreases GnRH secretion and mRNA levels.
Thus, reduction of 5α-reductase-1, by lowering allopregnanolone levels in the hypothalamus, might delay the increase in GnRH secretion required for pubertal onset.
A reduction in Srd5a1 expression is reported after many kinds of early life stress, and we showed that, besides the known repressive effect of cortisol on Gnrh mRNA levels, it also inhibited Srd5a1 expression. Our findings suggest that pre-pubertal exposure to immune challenges and the elevated stress response, affect reproductive function by modulating GnRH expression and release.

The Effect of RANKL on Differentiation of Murine Bone Marrow Mesenchymal Stem Cells to Adipocytes

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Introduction: Aging, Post-Menopausal and Steroid-Induced Osteoporosis are characterized by Increased Marrow Adipose Tissue (MAT) that is inversely correlated with Bone Mineral Density and Strength.
Recent data suggest that MAT is not a filler only, but participates in whole body energy metabolism.
Osteoporosis is associated with increased RANK-RANKL activity, and Anti-RANKL Antibody (Denosumab) is an effective treatment to reduce Osteoporotic fracture risk.
The increase in BMD induced by Denosumab may not be explained by its effect on osteoclasts only.
As Osteoblasts and Marrow Adipocytes Originate from a common Marrow Mesenchymal Stem Cell (MSC), Denosumab may affect the balance between Osteoblasts and Marrow Adipocytes.

Aim: To test the Hypothesis that RANKL induces Adipogenesis in MSCs in vitro.

Methods: Murine MSC C3H10T1/2 cells were induced to Adipogenesis in the presence of increasing RANKL concentrations.
The mRNA expression of Adipogenic Genes was determined by the comparative CT method.

Results: A significant increase in mRNA expression of the white Adipocytes markers aP2, C/EBPδ, and PPARγ was observed 72 hours after RANKL Treatment (1,5,10,100 ng/ml).

Conclusions: Our data suggest that RANKL increases the generation of white Adipocytes from MSCs. Thus, the favorable effects of Denosumab may include inhibition of MAT generation beyond its anti-resorptive effect.

Vasorin Involvement in Ovarian Angiogenesis

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The Ovary homes the Oocyte reservoir, each protected and nourished by the somatic Granulosa and Theca cells, comprising the follicle.
Folliculogenesis culminates with ovulation, which is a massive Angiogenic response.
Transforming Growth Factor-β1 (TGFβ1), a known signaling molecule involved in folliculogenesis, is negatively regulated by Vasorin.
Vasorin (Vasn), a Transmembrane protein, shed upon cleavage to the extracellular space, trapping TGFβ1 thus attenuating its activity, was found by us as a novel regulator of Folliculogenesis.
Specifically, using a Vasn conditional KO (cKO) mouse model, established in our laboratory, we demonstrated that Vasn is involved in regulating the size of ovulation.
In the present study, we Hypothesize that Vasn control of the Ovulatory response is mediated by TGFβ1 signaling and its effect on ovarian angiogenesis.
To explore our Hypothesis, we evaluated the Vasculature around growing follicles from antral stage, through Ovulation and corpus luteum formation.
We traced the Vasculature ex-vivo and in-vivo intra-vitally, employing an ovarian imaging window, established by us.
Our analysis revealed that ovaries of Vasn cKO mice exhibit a more pronounced level of vasculature then their WT siblings.
Mucification of Cumulus-Oocyte complexes, which is an essential prelude of ovulation, is also higher in cKO mice.
Our findings so far, support the role of Vasn in regulating the ovulatory response further suggesting that its action involves the vascular system.
As Vasn was found to be present in Human Follicular fluids aspirated from IVF patients, it may play a role in Human Folliculogenesis.

Direct Oral Antucoagulants Decrease Bone Formation in MC3T3-E1 Cells

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Background: The use of Anticoagulation is common in medical conditions such as Venous Thromboembolism, Atrial Fibrillation and Mechanical Heart valves.
Treatment with Heparin Derivatives and vitamin K Antagonists is rapidly being replaced with direct Oral Anticoagulans (DOACs), which have gained popularity due to their safety profile and easier surveillance. Therefore, an increasing number of young patients will be treated with these medications for the long term. Long-term Heparin Treatment is a known Risk factor for the development of osteoporosis.
The effect of DOACs on bone health has yet to be established.
Herein we address this paucity of information via in vitro studies examining the effect of DOACS on Osteoblast proliferation, differentiation and function in an Osteoblastic Cell line model.

Material and Methods: MC3T3-E1 cells were induced to Osteogenesis with β-Glycerophosphate and ascorbic acid. The effects of DOACs Apixaban, Rivaroxaban and Dabigatran at concentrations 0.013μg/ml (corresponding to blood concentration in treated patients) on cell survival was determined by XTT assay. Osteoblast differentiation and function were determined by alkaline phosphatase activity and mineralized nodule formation, respectively. Heparin (0.2U/ml) was used as positive control.

Results: No difference in cell survival between DOACs- and vehicle-treated cells was found.
Treatment with all DOACs significantly decreased (2-fold) alkaline phosphatase activity compared to vehicle-treated cells.
Impaired mineralized nodule formation was observed in DOACs-treated cells with a 3-fold decreased mineralization that was not significantly different from Heparin-Treated Cells.

Conclusion: Apixaban, Rivaroxaban and dabigatran adversely affect Osteoblast Differentiation and function in MC3T3-E1 cells.

The ADVICE4U STUDY: Opportunity to optimize insulin pump settings in children, adolescents and young adults with type 1 Diabetes using automated artificial intelligence system

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Objective: Decision support systems are emerging as a treatment tool for persons with T1D and healthcare members. Advice4U study aims to evaluate the safety and efficacy of DreaMed Advisor algorithm to frequently adjust insulin doses in young persons with T1D.

Research Design and Methods: 6-month, multicenter-multinational, parallel (2-arm), randomized controlled, non-inferiority study. 108 participants with T1D using insulin pump therapy and continuous glucose monitoring (CGM), ages ≥ 10 to 21 years, HbA1c 7-10%, were recruited. After 3-4 weeks of run-in period, participants were randomly assigned (by age and A1c) to either the Advisor arm or Physician arm. Insulin dose adjustments were made every 3 weeks, in both arms, based upon collection of adequate CGM and pump data uploads from home or during regular clinic visits. Primary efficacy endpoint is time within 70-180 mg/dl. Primary safety endpoint is time 54 mg/dl.

RESULTS: The study was conducted at 4 sites in the US and 3 sites in Germany, Slovenia and Israel. Generally, participants, families and health care providers were glad to participate in a study that allowed for sharing of glucose and insulin data frequently and remotely. In addition, healthcare team members were easily able to review the data and share dosing recommendations seamlessly.

CONCLUSIONS: The Advisor Pro can be used to optimize insulin pump setting during clinical visits, in-between visits or as part of virtual-telemedicine visit. The ease of use of the remote system can facilitate intensive diabetes care management that can offer frequent insulin adjustments aim to improve glycemic control.

Prurigo Pigmentosa - An Acute Complication of Ketogenic Diet

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A 22-year old female with type 1 diabetes (T1DM) presented with generalized rash.
She was diagnosed at the age of 9 years and is treated with Insulin pump and CGMS (continues Glucose monitoring sensors), her recent HbA1c was 7.4%.
Four weeks prior to her rash presentation she started a low carbohydrate Diet (50 gr carbs per a day) in order to improve her glycemic control.
Pruritic erythematous papules, papulovesicular, and vesicles appeared on her axillary region, upper back, and groins. Lesions were associated with severe pruritus and negatively affected her quality of life.
Various therapies were initiated by Dermatologist as: antifungal agent, Itraconazole, and Betamethasone Esters, without any improvement. Her serum betahydroxbutyrate levels were between 1.1-1.2 mmol/l.
Prurigo pigmentosa, a rare pruritic inflammatory dermatosis secondary to her high ketones levels was diagnosed.
Her condition resolved after she increased her carbohydrate intake to 75 gr per a day.
Beta-hydroxybutyrate level decreased concomitantly to 0.1-0.2 mmol/l.
When carbohydrate restriction was rechallenged, she agaoun entered Ketosis, followed by recuurrence of the pruritic lesions. Carbohydrate intake was increased and subsequently all lesions resolved with remaining reticuler Hyperpigmentatuin.
During the lasr few years low carbohydrate diet have gained popularity among patients with T1DM.
This case illustrates the rare side effect of high ketones body levels.
Health care providers should be familiar with this side effect.

Long Term Outcome of Appendical Neuroendocrine Neoplasms

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Introduction: Appendical Neuroendocrine Neoplasms (ANENs) are rare Tumors with an incidence of 0.15–0.6/100,000/year.
Data regarding optimal treatment strategy for these tumors is limited.

Aims: To describe ANEN characteristics, to evaluate their long-term outcome and to assess whether right Hemicolectomy influences outcome.

Methods: Clinical and Pathological data were obtained for patients diagnosed with ANEN who underwent surgery and/or follow-up in Meir Medical Center using electronic patient files.

Results: Sixty-five ANEN patients were included (69% females).
Mean age at diagnosis was 33 years (range 7-81) and the presenting symptom was acute appendicitis in 89%.
Tumor size was 15.4±13.9 mm and 55% were located at the tip of the appendix.
Higher risk tumor pathology was found in 38 patients including incomplete resection (5), subserosal fat invasion (24) and high risk histological subtype (10).
Nineteen patients (29%) underwent right hemicolectomy. Another 22 patients had clear or relative indication for right hemicolectomy (8 and 14 patients, respectively) according to international guidelines but underwent appendectomy only.
No mortality was recorded at the end of follow-up (median 8 years, range 1-23).
All patients remained tumor free except one who had an unusual presentation with an additional, synchronous, NEN of the left kidney and eventually developed Bone metastases.

Conclusion: Our findings indicate good prognosis in patients with ANEN regardless of the Pathologic characteristics or extent of surgery. In light of our results, revision of the indications for right Hemicolectomy is imperative.

Cartilage Specific K/O of SIRT1 Significantly Affects Bone Quality and Inhibits Catch Up Growth

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Spontaneous catch up growth (CUG) occurs when a growth restricting factor is resolved.
However, the efficiency of the CUG is not always sufficient and growth deficits remain permanent.
The therapeutic tool box for short stature is very limited, development of novel therapeutic means are urgent.

Aim &methods: In our nutritional induced CUG model, we found that the level of Sirtuin-1 (SIRT1) protein was significantly increased in food restricted animals and reduced during CUG. In order to study the role of Sirt1 in modulating the response of the growth plate (EGP) to nutritional manipulation, we created a specific knock out of Sirt1 in collagen type II chondrocytes.

Results: Although the transgenic mice (CKO) were generally heavier and had higher EGPs, their bones were shorter, probably due to the fact that the EGP was less organized, specifically at the resting and proliferative zones. Surprisingly, reduction in Sirt1 level in the chondrocytes had dramatic effect on bone mineralization, as found in micro CT analysis.
During food restriction and re-feeding induced CUG, CKO mice were less responsive to the nutritional manipulation and CUG was less efficient: while the control littermates corrected the food restriction induced growth deficit during the refeeding period, CKO remained shorter.

Conclusions: These results show that Sirt1 is important for normal regulation of the EGP, in its absence the EGP is less organized and CUG is less efficient. These results may suggest Sirt1 as a novel therapeutic target.

Gain-of-Function Variants in The Ubiquitin-Specific Protease 8 Gene (gof-USP8) Affect The Immune Microenvironment in Corticotroph-Derived Pituitary Adenomas (CPAs)

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Introduction: Gain-of-function USP8 variants (gof-USP8), detected in 30% of CPAs, are associated with a better post-operative remission rates compared to wild-type USP8 (wt-USP8) PCAs.
The cause for this distinct phenotype is unclear. Modulation of immune-response by USP8 was demonstrated in neuroinflammatory diseases, but not in tumors.

Aim: To study the association between USP8-status and CPAs Immune-Microenvironment

Methods:RNA-seq data of PCAs were analyzed. Quantification of immune-cells subtypes and their activation-states was performed using transcriptome-based signature-recognition algorithms and compared according to their gof-USP8 status.
Validation analysis, based on The Cancer Genome Atlas (TCGA) whole exome and RNA-seq data of other Cancer types, was performed.

Results:wt-USP8 Tumors were relatively “Hot Tumors” in terms of immune profile, compared with gof-USP8, reflected by higher immune-cells fractions (regulatory and other T cells, B cells, activated and non-activated macrophages, all p0.05).
Nevertheless, the immune-profile of gof-USP8 PCAs suggested immune activation: higher natural-killer (NK) cells activated/resting ratio and T-helper fraction and less resting dendritic cells (all p0.05). Pathway analysis enriched immune-related pathways: phagocytosis (p=0.00008) and toll-like receptor regulation (p=0.00001).

Only 5/170 non-pituitary tumors with USP8 variants were gof-USP, and had more activated-T-memory cells and less nonactive macrophages (pUSP8 upregulation correlated with lower regulatory-T-cells fraction (n=210, r=-0.3, p=0.0001).

Conclusions: Our data supports the immunosuppressive effect of USP8 in general, but a pattern of selective immune-activation was detected in CAPs with gof-USP8 variants.
The unique gof-USP8 variants in PCAs and their distinct immune-landscapes may explain the different clinical course.

1Gestational Diabetes Mellitus and Progression to Diabetes in Different Ethnic Groups in Israeli Population

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Background: Gestational Diabetes Mellitus (GDM) is a frequent metabolic disorder being a risk factor for future Diabetes Mellitus (DM). There is insufficient data on the incidence of DM after GDM in different ethnic groups in Israel.

Methods: A retrospective study was performed on a cohort including all pregnant women who had a 100g oral glucose tolerance test (OGTT) between 2007-2017 at Clalit-Health-Services in Jerusalem district. Data collection included demographic, clinical and biochemical variables, as well progression to DM during the trial period. Patients with previous DM or pre-diabetes were excluded. GDM and DM were diagnosed according to the American Diabetes Association criteria.

Results: During the described period, 9939 pregnant women had an OGTT. Mean age 29.9±5.4, and mean BMI 25.4±4.9. GDM was diagnosed in 12.6%. GDM prevalence was significantly higher in Arabic ethnic group compared to Jewish (17.3% Vs 10.6%, OR=1.6), in age 35 (OR=2), in patients with higher BMI (OR=1.05) and patients with high serum triglyceride levels.

During the trial period, 1.6% of the cohort developed DM. Incidence of DM was higher in patients with previous GDM (5% vs 1.1%). Multivariate analysis showed increased risk for future DM after GDM in: age 35 (OR=1.8), Arab ethnicity (OR=1.8), higher BMI (OR=1.1) and high serum cholesterol or Triglyceride levels.

Conclusion: Incidence of DM after GDM was 5% during the trial period. Specific risk factors for future DM after GDM include age and ethnicity. Routine Laboratory test follow-up may be considered after GDM, mainly in high-risk patients.

Fetal Anogenital Distance is Longer in Polycystic Ovary Syndrome Mothers

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Aim: Anogenital distance (AGD) is a biomarker for the prenatal hormonal environment. Scarce evidence exists regarding the effect of prenatal androgen exposure in mothers with polycystic ovary syndrome (PCOS) on the human fetal AGD. The aim of the study was to assess the prenatal sonographic measurement of AGD in fetuses of PCO mothers vs. the general population.

Materials and methods: AGD was measured prospectively in fetuses at 26-37 weeks of gestation, using 2D ultrasound, in an axial view, at the level of the fetal perineum. Data was compared to fetal AGD nomograms, and the Z score was evaluated. Maternal and fetal characteristics were analyzed.

Results: 27 PCOS mothers carrying singleton fetuses were recruited (12 females, 15 males). Mean gestational age at measurement was 31.2 weeks ± 3 days. Mean AGD, adjusted for gestational age and gender, was significantly higher in the PCOS (21.13mm±5.9mm) compared to the control (17.19 mm ±5.45mm) group, respectively, p 0.001. Mean AGD-PCOS centile was 86.04 (±18.22). Z score was not statistically different in the males (2.035± 2.1950) compared to the females (2.185± 1.3834). The AGD measured in fetuses of mothers with diabetes (52% of the study group) was significantly longer compared to the general population (19.74 mm ±4.8mm vs. 15.11mm±4.77mm p0.001).

Conclusions: This is the first report demonstrating a longer AGD in fetuses of mothers with PCOS. AGD may play a role as a biomarker of the intra-uterine androgen milieu, specifically in PCOS. Importantly, this might change the way we approach and treat PCOS pregnancies.

Persistent Medullary Thyroid Carcinoma: An Israeli Multicenter Study

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Objective: Medullary Thyroid Carcinoma (MTC) is a rare cancer for which long-term outcomes remain poorly understood. We investigated predictors of disease-outcome in a subgroup of persistent-MTC patients aiming to identify factors associated with indolent disease.

Methods: From 193 MTC patients treated during 1963-2016, 107 with persistent disease and 11.4±9.9 yrs follow-up were included. Clinicopathological data and treatment modalities were analyzed looking for predictors of outcome.

Results: The mean age was 46.5±18, 52% were males, and 78.3% sporadic. At diagnosis, 85% had stage IV (40% IVc), 90% LN metastases, 36% distant metastases, 48% multifocal disease and 56% ETE. The tumor size was 30±19 mm. Initial treatment included total thyroidectomy (88.8%), neck dissection (83.2%) and local EBRT (30%). Additional treatment given to 60% of patients included re-operation (31/64), ERBT (21/64), TKIs (26/64), and chemotherapy (7/64). Disease-related mortality (DRM) occurred in 26.1% patients at a median follow-up of 17 years. Long-term outcome was not predicted by gender, tumor size, disease extension, or additional treatments. DRM been more prevalent in patients with structural persistence at 1-year (76% vs. 13% biochemically only, p=0.001). At last visit, all survivors had persistent disease (23.8% biochemical only). While younger age (P=0.001) and neck dissection (p=0.04) appeared significant predictors, this was bias by 2-times longer follow-up.

Conclusions: We found structural persistence at 1 year to be an important predictor for DRM in persistent MTC. In addition, a large proportion of MTC patients have indolent disease for whom the low-risk status is still poorly understood.

Adaptation of Colon Cancer Cells to the Brain Microenvironment: The Role of IRS2

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Background: Brain metastases (BMs) from colorectal cancer (CRC) are the fourths leading cause of BMs, and their incidence is on the rise. Yet, mechanisms mediating the formation of BMs by CRC cells are unknown. A possible candidate is insulin receptor substrate-2 (IRS2), a cytoplasmic adaptor mediating effects of insulin and IGF-1 receptors. We aimed to explore the IRS2 role in the adaptation of CRC cells to the brain environment.

Methods: Analysis of FoundationOne database including clinical samples of 148 CRC BMs and 4292 CRC liver metastases (LMs). Three-dimensional (3D) model was generated using InSphero assay. Human astrocytes conditioned media (HA-CM) or HA were used to create an in-vitro system mimicking the brain microenvironment. Intracranial CRC BMs mouse model was used.

Results: IRS2 was amplified in 13% of BMs, compared to only 3% of LMs (p0.0001). Moreover, IHC of human clinical samples showed increased expression of IRS2 in BMs compared to LMs.

IRS2-overexpressed CRC cells survived better in HA-CM and had enhanced 3D sphere formation in co-culture with HA, whereas IRS2-silenced CRC cells survived less in HA-CM.

Furthermore, IRS2 expression altered the cells` metabolism - IRS2-overexpressed CRC cells survived better upon glucose starvation, whereas IRS2-silenced CRC cells survived less. IRS2 expression altered AKT signaling pathway; hence, IRS2-overexpressed cells showed enhanced AKT phosphorylation under IGF-1 or HA-CM stimulation, whereas IRS2-silenced cells showed the opposite.

Finally, IRS2-overexpressed CRC cells formed larger brain lesions compared to control.

Conclusions: These data indicate a role for IRS2 amplification, in promoting the formation of BMs in CRC.

Increased BMI is Associated with Anti PD-1/PD L1-Induced Thyroid Immune-Related Adverse Events

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy, however, are associated with immune related adverse events (irAEs). Obesity is a pro-inflammatory metabolic state that may play a role in the development of irAEs.

Hypothesis: We hypothesized that likelihood of developing thyroid irAEs following anti-PD-1/L1 therapy increases with increasing body mass index (BMI).

Methods: We retrospectively analyzed data of 187 cancer patients who initiated anti-PD-1/L1 at our institution between 01/2014-12/2018, had normal thyroid function tests at baseline and had baseline BMI data available.

Results: Overall, 97 (52.2%) patients were with low-normal BMI (2), 52 (28.0%) overweight (≥25-30 kg/m2) and 37 (19.9%) obese (≥30 kg/m2). Thyroid dysfunction (hyper or hypo, overt or subclinical) developed in 72/187 (38.7%) patients, of whom 29/97 (29.9%) had low-normal BMI, 22/52 (42.3%) were overweight and 21/37 (56.8%) obese (p=0.14). With every 1 kg/m2 increase in BMI, the likelihood of thyroid dysfunction increased by 8.8% (p=0.004). Overt hyperthyroidism occurred in 32/186 (9.1%) of the patients – in 4.1% of patients with low-normal BMI, 11.5% of overweight patients and 18.9% of obese (p=0.006). Overt hypothyroidism occurred in 32/186 (17.2%) of the patients and was not significantly associated with BMI. Hyperthyroidism followed by overt hypothyroidism, consistent with thyroiditis, occurred in 13/186 (7.0%) of patients and was significantly associated with increasing BMI category (p=0.03).

Conclusions: Increased BMI was associated with increased thyroid irAEs in patients treated with PD-1/L1 inhibitors. Further exploration of the interaction between obesity and immunotherapy may provide insight into the role of inflammation in mediating immune response.

Subclinical Hypothyroidism in Pregnancy – Do Different TSH Cutoffs Predict Peripheral Hormones Change?

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Introduction: Subclinical hypothyroidism in the first trimester of pregnancy is defined as an elevated TSH above 2.5 or 4.0 mIU/l with a normal FT4 according to different guidelines.

Aim: To assess thyroid function tests in the first trimester and evaluate FT4 and FT3 levels in relation to TSH specific cut-offs (TSH 0.1,0.11-2.5,2.51-4, 4.1-10, 10 miu/l).

Methods: Retrospective study utilizing the Clalit Health Service, Jerusalem district database. 29,362 women with a positive bHCG measurement at time of TSH, FT4 or FT3 measurements with a subsequent live birth were analyzed.

Results: FT3 and FT4 levels were identical in the TSH 2.5-4.0 and 4.0-10 groups, but were significantly lower in the TSH10.0 group compared to the TSH

Conclusion: A TSH above 2.5 or 4.0 miu/l does not predict a significant decrease in FT3 or FT4 in comparison to a TSH of 4 -10. Current international guidelines should be reevaluated with reference to FT3 and FT4 levels.

The Effect of PCSK9 Inhibitor EVOLOCUMAB on Aldosterone among High Cardiovascular Risk Patients

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Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors decrease the degradation of low-density lipoprotein (LDL) receptors, thereby increasing the removal of LDL particles from the blood and significantly reducing LDL cholesterol levels by an average of 65%. Blom et al. showed changes in vitamin E, adrenocorticotropic hormone (ACTH), cortisol, total testosterone, and estradiol in EVOLOCUMAB (PCSK9 inhibitor)-treated patients (1). There are currently no published data on the impact of PCSK9 inhibitor monotherapy on aldosterone.

Aim of the study: To examine the effect of EVOLOCUMAB monotherapy on LDL cholesterol reduction and steroidogenesis in high cardiovascular risk patients with statin intolerance.

Methods: Lipid profile, sodium, potassium, aldosterone, cortisol, and ACTH were analyzed at baseline and after 3 months of EVOLOCUMAB therapy. Each participant underwent two dynamic tests, a 250 mcg ACTH test and an ambulation test, on two consecutive days at the beginning and end of the study.

Results: Fifteen patients were included in the study. Total cholesterol, LDL cholesterol, lipoprotein (a), and stimulated aldosterone levels were significantly lower after 3 months of EVOLOCUMAB therapy. There were no significant changes in ACTH, cortisol, or potassium levels.

Conclusions: Reduction in stimulated aldosterone secretion by EVOLOCUMAB treatment could theoretically be associated with the reduction of cardiovascular events, and that possibility warrants further investigation.

Reference:

1. Blom DJ, Djedjos CS, Monsalvo ML, Bridges I, Wasserman SM, Scott R, Roth E. Effects of Evolocumab on Vitamin E and Steroid Hormone Levels Results From the 52-Week, Phase 3, Double-Blind, Randomized, Placebo-Controlled DESCARTES Study. Circ Res. 2015 Sep 25;117(8):731-41.

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All-cause Mortality among Patients with Von Hippel-Lindau Disease and Pancreatic Neuroendocrine Tumors

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Introduction: Von Hippel-Lindau disease (VHL) is a hereditary multi-neoplasm syndrome, associated with an increased risk for retinal and/or central nervous system hemangioblastoma (HB), pancreatic neuroendocrine tumors (PNETs), renal-cell carcinoma (RCC), pheochromocytoma and additional neoplasms. VHL diagnosis is based on family history of VHL and one VHL-related manifestation. Additional criteria include detection of two HBs or one HB and visceral neoplasm ("International" Criteria), or detection of any two VHL-related manifestations (the Danish Criteria).

Aim: To assess the impact of diagnosis with PNET in patients with VHL, on their risk for all-cause mortality (ACM).

Methods: Retrospective analysis based on the Surveillance, Epidemiology and End Results database, including patients diagnosed with HB, RCC, PNET or pheochromocytoma. VHL diagnosis was determined according to the international/Danish criteria. Risk for ACM was compared among patients with VHL, with/without detection of PNET.

Results: Among 28,029 patients (age at diagnosis 62.9±11.9 years, 12,336 [44%] women),159 (0.6%) were diagnosed with VHL, defined by co-diagnosis with RCC (93.4%) and/or HB (8.9%). Patients were younger when diagnosed with VHL-related PNET (54.0±14.0 years) vs. sporadic PNET (60.2±13.0 years, p0.001). Survival analysis of the entire cohort demonstrated a higher risk for ACM among patients with vs. without PNET (Log-rank test, p=0.014). However, stratification according to VHL diagnosis status demonstrated a higher ACM risk among non-VHL patients, with vs. without PNET (p=0.024) whereas among patients with VHL, ACM risk was comparable between patients with vs. without PNET (p=0.94).

Conclusion: Diagnosis with PNET is not a risk factor for ACM in patients with VHL.

Sex-dependant Response to Circadian Disruption in Diurnal Sand Rats

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Most studies on physiological functions and pathologies are conducted on males of nocturnal mice and rats. However, diseases such as depression, type 2 diabetes (T2DM) and cardiovascular diseases in humans (diurnal), show different prevalence and characteristics in females and males.

Aim: Compare the effects of short photoperiod (SP) vs. neutral photoperiod on behavior, glucose tolerance, daily glucose rhythm, body weight and heart weight in male vs. female fat sand rats (Psammomys obesus).

Methods: We used male and female fat sand rats, a diurnal, widely-used animal model for T2DM. Animals were provided with ad-lib tap water and standard rodent diet and acclimated to short photoperiod (SP; 5hr light/ 19hr dark, N=34) or to neutral photoperiod (NP; 12hr light/ 12hr dark, N=38). Animals were weighed and tested for glucose tolerance, depression-like behavior in the forced swim test (FST), 24-hour blood glucose levels, and finally euthanized, and the hearts were weighed.

Results: On average, males showed higher levels of depression-like behavior, lower glucose tolerance, and higher heart/total weight ratio than females. Under SP acclimation, males increased depression-like behavior, and decreased glucose tolerance, with no effect on heart/total weight. In contrast, females showed increase in heart/total weight, with no effect on depression-like behavior, or on glucose tolerance.

Conclusions: Males and females show differences in behavior, glucose tolerance, daily glucose rhythm, body weight and heart weight in response to circadian disruptions. Additional research with females is required to delineate the sex-dependent effects, and promote sex-based health care, prevention measures and therapies.

The Quantitative Relationship between Autonomous Cortisol Secretion, Dysglycemia and the Metabolic Syndrome

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Objective: Autonomous cortisol secretion (ACS) is the most common endocrine abnormality in the evaluation of adrenal incidentalomas. The categorization of ACS is derived from a 1 mg dexamethasone suppression test (DST). Impaired DST is associated with several metabolic derangements. In this study we assess the correlation between post-DST cortisol level, analyzed as a continuous parameter, and indices of glycemic metabolism.

Study design: We prospectively collected data of 1976 patients evaluated for adrenal incidentalomas in a large tertiary medical center between December 1st, 2017 and August 31st, 2019. 73 patients completed the evaluation process. Post-DST cortisol levels were analyzed for correlation with various metabolic parameters, including fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) among the general cohort and for subgroups stratified by the number of metabolic syndrome (MS) criteria.

Results: Post-DST cortisol demonstrated a linear correlation with FPG and HbA1c across its entire cortisol range (R=0.51 and 0.41, respectively, p≤0.01). The correlation between post-DST cortisol and FPG was strengthened with increased number of metabolic syndrome criteria. Patients with 4 MS criteria show a stronger correlation (R=0.92) compared to patients with only a single criterion (R=0.509). Furthermore, mean post-DST cortisol levels increased as the number of MS criteria accumulated.

Conclusion: Post-DST cortisol should be viewed as a continuous parameter in risk stratification algorithms for development of the MS and particularly dysglycemia.

Difficulties in Utilization of Improved Glucose Monitoring in Type 1 Diabetics

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In 2010, CGM were introduced into the Israeli Health basket for type 1 Diabetics under age 18.
In 2012, the basket was extended to include CGM for adiult type 1, who experienced at least two major hypoglycemic events.
Since then attempts to extend the package have been unsuccessful.
In 2016, Abbot introduced a new Technology, flash Glucose monitoring called Libre.
In 2018 the Libre was included in the basket for all Type 1 above age 18.

As published in Diabetes Care and BMJ open Research and Care (both 2019), use of the Libre in Diabetics has had a positive effect on quality of life: less Hypoglycemic events and better Glucose control.
As reported 11% of patients have Skin reactions with less than 1% necessitated discontinuation of Libre.
Our aim was to evaluate the effects of Skin reactions on the discontinuation of the Libre and our purposed effect on Legislation.

Results: From 2018 -2019, in Meuhedet`s Kiryat Sefer, Ramla and Rehovot Clinics, five patients were identified with allergies to the Libre (5.8%) which necessitated cessation of use.
Others experiended sensitivity circumvented with Skin barriers. This is compatible with literature.
One of the patients was very allergic to the Glue on the transmitter and also to medetronic transmitter but not to Dexcom.
Since he was not elligible for other CGM, he removed the glue and replaced it with different adhesive.
We recommend changes in Health basket which will allow alternatives for those allergic to the Libre or other CGM devices Allergic reaction.

Biomarkers of Acute Kidney Injury in Diabetic Patients Treated with SGLT2 Inhibitors

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Background: Inhibitors of Sodium-Glucose co-transporter-2 (SGLT2i) were found to improve renal outcome in Diabetic patients in large prospective randomized trials.
Yet, SGLT2i may acutely reduce kidney function through volume depletion, altered glomerular Hemodynamics or intensified medullary Hypoxia leading to acute Tubular Injury (ATI).
The aim of this study was to prospectively assess the Pathophysiology of acute kidney Injury (AKI) in patients Hospitalized while on SGLT2i, differing ATI from pre-renal causes using renal biomarkers.

Methods: Serum and urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Ischemia Molecule (KIM)-1 were determined in 46 Diabetic patients who were on SGLT2i upon Hospitalization with an acute Illness.

Results: Serum and urine NGAL, but not KIM-1, were significantly increased in 21 of the patients who presented with AKI upon admission, as compared with 25 patients that maintained Kidney function.
Both serum and renal NGAL correlated with the degree of renal impairment, which in many cases was likely the result of additional acute renal perturbations, such as Sepsis.

Conclusions: Increased Urinary and Serum NGAL indicates that ATI, principally affecting Distal Tubular segments, may develop in some of the patients hospitalized with an acute illness and AKI while on SGLT2i. It is suggested that intensified medullary hypoxia by SGLT2i might be detrimental in this injury. By contrast, concomitantly unaltered KIM-1 might reflect improved deep cortical oxygenation by SGLT2i, and may explain an overall reduced risk of AKI with SGLT1i in large series.
The independent potential of SGLT2i to inflict medullary hypoxic damage should be explored further.

Course of Puberty and Growth Spurt in Boys with Type 1 Diabetes

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Inadequate glycemic control in children with type 1 diabetes mellitus (T1D) can hinder their sexual development and associated growth spurt.

Aim: To study the course of puberty, pubertal growth and final height (F-Ht) in boys with T1D, and factors affecting these.

Methods: Included were 68 boys diagnosed with T1D who were pre-pubertal at diagnosis and had completed puberty. Collected were clinical and anthropometric data from diagnosis to F-Ht. F-Ht was compared to parental height and to the data of the national health survey

Results: –F-Ht-SDS was lower than Ht-SDS at diagnosis. It was similar to parental Ht-SDS and to that of the national health survey (p=0.126). F-Ht was inversely related to average HbA1c during puberty (R=-0.27, p=0.045). Boys who presented with diabetic ketoacidosis at diagnosis were shorter than those who did not throughout the entire follow-up. Age at onset of puberty was significantly related to the age of maternal menarche (R=0.44, p=0.01) and to HbA1c levels in the year preceding puberty onset (R=0.36, p=0.01). Total pubertal growth was inversely related to HbA1c levels in the year preceding onset of puberty (R=-0.3, p=0.03)

Conclusions: Boys with T1D diagnosed before puberty achieve F-Ht similar to that of their parents and of the general population. Diabetic ketoacidosis at the diagnosis is associated with diminished F-Ht. Age of pubertal onset and F-Ht are affected by genetic factors and by glycemic control before and during puberty. These results emphasize the importance of tight metabolic control in adolescents, to enable growth within the genetic target.

BMI and Mortality in Surgical Patients – Is Higher Better?

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Objective: Investigate the association between body mass index (BMI), length-of-stay (LOS), and mortality in patients with and without diabetes mellitus (DM), hospitalized to general surgical wards.

Methods: Historical prospectively collected data of patients hospitalized between January 2011 and December 2017. BMI was classified as follows: underweight (18.5), normal weight (18.5-24.9), overweight (25-29.9), obesity (30-34.9) and severe obesity (≥35). Main outcomes were LOS, 30-day and end-of-follow-up mortality.

Results: The cohort consisted of 27,639 patients (mean age 55±20 years; 48% male; 19% with DM). Mean LOS was longer in DM, compared to non-DM patients (5.9±2.7 vs. 4.4±1.7, respectively), with longest LOS among underweight patients. 30-day mortality was 2% of non-DM (371/22,297) and 3% of DM patients (173/5,342). In DM patients, 30-day mortality risk showed a step-wise decrease with increased BMI: 10%, 6%, 3%, 2%, and 1% for underweight, normal weight, overweight, obese and severely obese patients, respectively. In non-DM patients, 30-day mortality risk was 6% for underweight, 3% for normal BMI and 1% across the overweight and obese categories. Mortality rate at the end-of-follow-up was 9% of non-DM and 18% of DM patients (aOR=1.3, 95% CI, 1.2-1.5). In DM patients, higher BMI category was associated with decreased mortality: 52%, 29%, 17%, 14%, and 7% with underweight, normal weight, overweight, obesity and severe obesity, respectively, with similar trend in non-DM patients.

Conclusions: Among patients with and without DM admitted to surgical wards, BMI has an inverse association with short- and long-term mortality. Our findings demonstrate the 'obesity paradox' in the general surgical population.

Adrenocortical Carcinoma – A Tertiary Center`s Recent 5-year Experience

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Background: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with poor prognosis. The aim of this study was to characterize patients diagnosed with ACC at a single center between 2014-2019.

Methods: We retrospectively reviewed data regarding demographics, tumor characteristics, functionality, treatment and survival.

Results: The study cohort included 27 subjects (56% females), followed for 27±10.6 months. The mean age at diagnosis was 49.4±9 years. Co-morbidities at presentation included hypertension (63%), DM (22%) and dyslipidemia (26%). 74.1% of tumors were functioning – of which 85% were cortisol-secreting and 15% androgen-secreting. Aldosterone was secreted additionally in 15%. ENSAT stage at diagnosis was stage 1 in 15%, stage 2 in 35%, stage 3 in 12% and stage 4 in 38%. 89% of patients underwent surgery. Treatment with mitotane was initiated in 82% of patients, reaching a mean maximal dose of 3.3 ±0.4 grams/day. Chemotherapy or radiation were given in 37% and 22%, respectively. Several patients (14.8%) had a second primary cancer, diagnosed before ACC in 75%. Progression was observed in 48% of patients, with a progression-free survival of 8.3±6.6 months. 35% of patients died during follow-up, time to death was 12.8±0.4 months. 22% of patients survived over 30 months after diagnosis. KI67 above 20% or stage above 2 negatively affected survival.

Conclusions: ACC remains a rare disease with poor prognosis. However, it is a heterogeneous disease, with some patients achieving survival of over 30 months. Further characterization of these patients may improve our understanding of the biology and treatment of this rare disease.

Inferior Petrosal Sinus Sampling – 16 Years of Experience from A Single Tertiary Center in Israel

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Introduction: IPSS (Inferior petrosal sinus sampling) is a reliable test for differentiating between Cushing's disease and ectopic ACTH secretion.
For the last 30 years, IPSS is performed in Israel only at Hadassah Ein Kerem Medical Center.

Methods A retrospective study including all patients who underwent IPSS for whom electronic data were available. Medical records were reviewed, and additional information was collected from the referring endocrinologists.

Results: 63 patients underwent IPSS between 2003 and 2019.
The most common indications were the absence of a visible pituitary adenoma on MRI (43 patients), inconclusive biochemical testing regarding ACTH source (16 patients), and persistent Cushing's syndrome after prior pituitary surgery (12 patients).
17 patients had more than one indication.

IPSS test results indicated pituitary ACTH secretion in 52 patients, of which 47 underwent pituitary surgery: 31 were biochemically cured whereas 13 had residual or recurrent disease.
5 patients did not undergo surgery.
In 11 patients test results were consistent with ectopic ACTH secretion.
4 patients were found to have a documented ACTH secreting ectopic tumor, 3 had an adrenal adenoma, in 2 patients the source of ACTH was not found, and 2 underwent pituitary surgery despite IPSS, and recovered. We were unable to obtain any further clinical information regarding these patients.

No major complications were documented.
4 patients had a groin Hematoma, and one had elevated Blood pressure during the procedure.

Conclusions: IPSS in Israel is a feasible, safe, sensitive and specific method for the evaluation of ACTH dependent Cushing's syndrome.

Characteristics of Hypothyroid Patients Achieving Long Term Euthyroidism on Levothyroxine Treatment

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Introduction: Hypothyroid patients on Levothyroxine therapy often experience fluctuations in TSH.

Aim: To assess the association between biochemical and clinical characteristics and long-term TSH normalization under Levothyroxine treatment.

Methods: A retrospective nested case-control study including hypothyroid patients above age 18 insured by Clalit Health Service (CHS) in the South between 2002-2017, with pre-treatment TSH, who purchased Levothyroxine for at least 5 consecutive years with annual on-treatment TSH. Thyroidectomy, iodine ablation or congenital hypothyroidism were exclusion criteria. Cases had a TSH level within the normal range for 5 consecutive years, while the others served as controls. Demographic, laboratory, pregnancy status and pharmacy purchase were extracted from the computerized medical records of CHS and compared between the groups.

Results: Out of 5472 patients included, 644 had a normal TSH for 5 consecutive years (11.8%, cases). Cases and controls differed in mean age at first levothyroxine purchase 55.8±13.7 and 54.10±16.2 (p=0.003), percent females 84.8% and 81.4% (p=0.035), mean pretreatment TSH 5.15±9.6 and 10.02±29 (p0.001), thyroid autoantibody positivity 36.5% and 56.7% (p0.01) and rates of pretreatment subclinical hypothyroidism 44.4% and 54.6% (p0.001). In multivariable logistic regression the odds ratio of normal TSH for 5 consecutive years was 0.99 for pretreatment mean TSH (p=0.89), 0.48 for positive thyroid antibodies (p0.001), 0.72 for pretreatment diagnosis of subclinical hypothyroidism (p=0.032), 0.69 for use of iron supplements and 1.01 for age at first levothyroxine purchase (per year, p=0.02).

Conclusions: Positive thyroid autoantibodies, pretreatment subclinical hypothyroidism and use of iron supplements lowered probability of long term TSH normalization.

Zebrafish GnRH Neurons Communicate Synaptically to Control the Assembly of the Circuit

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Migration of GnRH Neurons from their birthplace in the olfactory epithelium al ensembles in which GnRH Neurons are active as populations rather than individually.

Early during development, clustered GnRH Neurons form a functionally isolated, spontaneously active circuit that is internally wired through monosynaptic glutamatergic synapses into which newborn Neurons integrate before entering the brain.

This initial phase of integration drives a phenotypic switch which is required for GnRH cells to properly migrate towards their hypothalamic destination. Our data suggest that cooperativity between active GnRH Neurons is mandatory for their developmental migration.

Positive Modulation of SSTR2 Expression in a Neuroendocrine Tumor Model - Aiming towards Improving the Efficacy of Somatostatin Analogues Therapy

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Background: Neuroendocrine Neoplasms (NENs) are rare and heterogeneous Tumors, most of them diagnosed at an advanced stage of metastatic disease.
Somatostatin receptors (SSTR), expressed in 85% of NENs cells, are a pivotal target for either somatostatin receptor imaging (SRI) or for treatment with either regular/cold or radiolabeled somatostatin receptor analogues (SSA).
SSTR2, the most frequent SSTR expressed by NENs cells, has the highest affinity for SSA. However, some NENs patients have a weak SSTR expression on tumor cells, with limited uptake on SRI.
Interferon-α (IFN-α) has been used as biotherapy for NENs; interestingly, there are some clinical observations suggesting an increased uptake on SRI after IFN-α treatment, however, the underlying mechanism is unknown.

Methods: SSTR2 expression was measured by RT-PCR in two NENs cell lines treated with increasing concentrations of IFN-α.
Four sites, upstream and downstream of SSTR2 promoter, were identified as enhancers`location by bioinformatics analysis with an IGV browser and suspected to be IFN-α binding sites.
The four fragments Enh1-4 were cloned to PGL4.23 plasmid, followed by a Luciferase reporter assay.

Results: IFN-α induced upregulation of SSTR2 mRNA in both NENs cell lines.
The Luciferase reporter assay with HEK293T cells showed increased Luciferase activation in Enh1, which was further increased following IFN-αt.

Conclusion: IFN-α leads to upregulation of SSTR2 mRNA levels.
We suspect that the Enh1 region contains a binding site of IFN-α responsible for the upregulation of SSTR2.
Further investigation to understand the exact mechanism and the transcription factors involved in this phenomenon is warranted.

Plasma Hemoglobin Levels at Baseline and Follow-up as a Prognostic Marker for Progression and Mortality in Patients with Pancreatic Neuroendocrine Tumors (PNET)

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Introduction: Patients harboring PNET typically have heterogenous disease course, despite comparable patient characteristics and PNET grade and stage.

Aim: To test the utility of Hemoglobin (Hb) for risk stratification of patients with PNET.

Methods: Retrospective analysis of patients diagnosed with PNET between 1995-2019.
Data retrieved included demographics, tumor-related parameters, imaging follow-up and survival.
Hb dynamics were calculated as current/baseline ratio.
Univariate and Kaplan-Meier analyses were performed.

Results: Sixty-seven patients with PNET were included in the analysis (mean age at diagnosis 63.12±11.83 years, 43.3% women).
Patients cured (n=20) had higher baseline (13.24±1.77 vs. 12.10±1.89 gr%, p=0.035) and current (12.96±1.84 vs. 11.17±1.87 gr%, p=0.002) Hb levels compared with patients with persistent disease. Similarly, patients without vs. with disease progression had higher current Hb levels (12.76±1.65 vs. 10.71±1.85 gr%, p0.001, respectively) and trend of higher current/baseline Hb ratio (1.01±0.16 vs. 0.91±0.19, p=0.054, respectively). Additionally, patients deceased vs. alive at last follow-up had lower current Hb levels (9.76±1.72 vs. 12.17±1.85 gr%, p=0.001).

In Receiver Operator Characteristics (ROC) curve analysis, current Hb levels had high area under the curve for both progression (0.806) and mortality (0.831). Survival analysis demonstrated marginally increased risk for progression (p=0.088) and mortality (p=0.093) among patients with lower current Hb levels. Furthermore, lower current/baseline Hb ratio was associated with higher progression and mortality risks (p=0.0095 and p=0.037, respectively).

Conclusions: Current Hb levels and Hb dynamics during follow-up may serve as a surrogate marker for progression and mortality risk in patients with PNETs.

CB1 Receptor Regulates Renal GLUT2 Expression and Function via mTORC1 Signaling Pathway

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Introduction: Diabetic Kidney Disease (DKD) increases the risk for morbidity and mortality in patients with diabetes.
Recently, we demonstrated that activation of Cannabinoid-1 Receptor (CB1R) in renal proximal Tubular Cells (RPTCs) results in Upregulation of Glucose Transporter 2 (GLUT2), which, in turn, contributes to RPTCs dysfunction and to the development of DKD.
Hyperglycemia also Increases the expression and activity of CB1R and the mammalian target of Rapamycin complex 1 (mTORC1).

Aim: To decipher whether CB1R regulates GLUT2 via mTORC1 signaling pathway in RPTCs.

Methods: By using a Multidisciplinary approach, including Pharmacological and genetic Manipulations of CB1R, mTORC1, and GLUT2, we assessed the effect of CB1R activation/inhibition on mTORC1 activity and GLUT2 expression under conditions of acute and Chronic Hyperglycemia in Human RPTCs and Akita-Diabetic mice, respectively.

Results: Acute exposure of RPTCs to high Glucose resulted in activation of the CB1R by its endogenous ligands (endocannabinoids) and consequently upregulation in GLUT2 expression.
This was associated with increased AKT Phosphorylation and enhanced mTORC1 activity (measured by S6 phosphorylation) in a Gi and PI3K dependent manner.
Similarly, chronic exposure to Hyperglycemia in Akita mice markedly induced mTORC1 activity, along with increased GLUT2 expression in RPTCs; effects that were prevented in Akita RPTC-CB1R null mice.
Moreover, specific deletion of GLUT2 in RPTCs ameliorated DKD in Akita mice, emphasizing the key role of GLUT2 in the development of DKD.

Conclusions: Our results highlight the key role of CB1R-mTORC1 signaling pathway in regulating GLUT2 in RPTCs, and in mediating the development of DKD.

Gender Differences in the Presentation, Course and Outcomes of Primary Hyperparathyroidism

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Introduction: Primary hyperparathyroidism (PHPT) is more prevalent in women than in men. The few studies on gender-associated differences in PHPT were cross-sectional.

Methods: A retrospective study on consecutive 182 women and 161 men with PHPT monitored at a large endocrine institute for 6.27±5.45 years. Relevant data was retrieved from the computerized files and compared between men and women throughout the follow-up period in the whole cohort and within two subgroups of patients diagnosed 50/≥50 years.

Results: Male and female PHPT patients were diagnosed at a similar age (56.5/ 58.7 years, respectively), with similar levels of serum calcium (10.9/10.8 mg/dl), 25-hydroxy-vitamin D (66/74nmol/L), PTH, and urine calcium (307/269 mg/24h). Male patients had higher maximal levels of serum calcium than females (11.8/11.4 mg/dl). Nephrolithiasis was more frequent in males (33% vs 21%, p=0.01), whereas females had higher prevalence of osteoporosis (65% vs 45%, p0.001). Women had lower mean spinal T-score at PHPT diagnosis. At last visit, women demonstrated worse BMD results in all sites, and had more fractures than men (34% vs 20%, p=0.004), despite receiving medications for osteoporosis more often and for longer periods. Parathyroidectomy was performed in 42% of males and 52% of females. All the gender-associated differences were statistically-significant only in patients diagnosed at age ≥50 years.

Conclusion: Osteoporosis is the most common clinical sequela of PHPT in both genders. Women receive more intensive pharmacological treatment and undergo parathyroidectomies more often, but still, have worse outcomes of osteoporosis than men. Fractures occur in one third of PHPT female patients.

Distinct Prognostic Factors in Sporadic and Multiple Endocrine Neoplasia Type 1 (MEN1)-Related Pancreatic Neuroendocrine Tumors

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Background: Pancreatic Neuroendocrine Tumors (PNET) may develop sporadically or in the context of hereditary syndrome. In patients with multiple endocrine neoplasia type 1 (MEN1), PNET is the main cause of Death.

Aim: To compare the mortality risk in sporadic and MEN1-Related PNETs, and Identify High-Risk Populations.

Methods: Retrospective SEER database analysis of patients with PNET.
Patients with MEN1 were defined by syn/metachronous pituitary adenoma.
Clinical data were obtained, and all-cause mortality (ACM) risk was compared in univariate and Multivariable Analyses.

Results: The cohort included 362 patients (47% women) with sporadic (n=337) and MEN1-related (n=25) PNETs. Patients with MEN1 were younger when diagnosed with PNET (51.2±15.8 vs. 60.8±13.1 years, p=0.001).
Patients with MEN1 and well-differentiated (WD) PNET had a trend towards a Higher mortality risk vs. sporadic WD PNET (Log rank test, p=0.09).
Among patients with distant metastasis, ACM risk was higher in the MEN1 vs. sporadic groups (p=0.002).
Among those with large (4 cm in diameter) primary PNET, MEN1 group had higher ACM than sporadic (p=0.001), even when analysis was limited to localized disease (p=0.006).
Multivariable analysis, adjusted for age, gender, stage, grade and Surgery Defined MEN1 diagnosis (hazard ratio [HR] 3.37, p=0.029) and Male gender (HR 1.67, p=0.037) as Independent Risk factors for poor prognosis.

Conclusion: MEN1-related PNETs confer higher risk for ACM than sporadic PNET, specifically among patients with advanced disease and large primary Tumors.
Our results demonstrate the unique biological behavior of PNETs in the context of hereditary syndrome, necessitating expertise and syndrome-specific screening and management plan.

Falling Insulin Requirements in Women with Pregestational Diabetes

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Background: Previous studies evaluating the association between falling insulin requirements (FIR) during late pregnancy and adverse maternal and neonatal outcomes yielded controversial results.

Methods: We conducted a retrospective cohort analysis of data collected from women delivering at Shamir Medical Center between 2008-2018. The percent of FIR was calculated by dividing the lowest total insulin dose that was measured after the peak insulin dose (the highest total insulin dose per day during the third trimester) by the highest insulin dose. We compared the composite outcome of Cesarean-section due to fetal distress, pre-eclampsia, induction of labor due to intra-uterine-growth-retardation, small-for-gestational-age or fetal acidemia in women with FIR 15% to those with FIR 15%.

Results: In the final analysis, were included 87 pregnancies in 80 women, 31% of them had T1DM. Sixteen (18.4%) women had a more than 15% FIR during the 3rd trimester. Women with FIR 15% had lower pre-gestational body mass index (BMI) at baseline (24.9±4.43 vs. 28.16±5.79 kg/m2 p=0.049). Women having 15% FIR had significantly more hypoglycemic episodes during pregnancy. Composite outcome occurred in 5 (31.3%) deliveries in women with FIR 15% and in 29 (40%) of deliveries in women with FIR 15% p=0.47. There were no significant differences in all other maternal or neonatal outcomes.

Conclusions: FIR during the 3rd trimester occurs in a considerable number of diabetic women. In our cohort of women with pregestational diabetes, this was associated with increased risk for maternal hypoglycemia during pregnancy but not to other adverse maternal or neonatal outcomes.

Reversibility of Type 1 Diabetes Mellitus. Myth or reality? A proof- of concept.

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Protection and preservation of residual β-cell function in T1DM are of the highest priority because even miserable amounts of endogenous insulin are critical for maintaining proper diabetes control and complications avoidance.
The current study is a proof- of - concept of our new approach to T1DM, viewing the disease as a primary impairment of nervous system.
We developed and patented the triple adjacent therapy in T1DM patients.

Methods: We report a two-year retrospective analysis of 56 Type 1 Diabetes (T1DM) patients treated with a combination of DPP4i, PPi, GABA. 19 of them fulfilled the protocol criteria.
Parameters “Before-and-After” were compared.
We also developed the “T1DM probability score”.
Patients with more than five points were considered to suffer from T1DM.

Results: HbA1c decreased from 8.6±2.1 to 6.5±1.1 % (p-0,001).
Insulin demands reduced from 26.0±23.4 to 10.8±14.4 units per day (p-0,003).
BMI was stable: 23.4±2.5 kg/m2 before vs. 23.0±2.5 kg/m2 after (p-0,28).
CGM showed Hypoglycemia TIR: 1.9±2.6 % vs.6.3±11.4 % (p-0,50).
Normoglycemia TIR: 56,5± 32,8 vs. 62,1± 29,2% (p-0,064).
Hyperglycemia TIR 41.6±33.1 vs. 31.6 ± 30.5% (p-0,02).
Six patients (31.6%) stopped their insulin Injections for at least 26 weeks’ period.
Only one patient returned to insulin injections after 26 weeks.

Conclusions: This study demonstrates the efficacy of proposed therapy in T1DM.
31.6% of participants entered a long-term remission and became Insulin – free.
All-in – all, this study is a proof of our concept.

Endothelial Vascular Adrenal Cyst with Unusual Presentation

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Primary adrenal cysts are a relatively rare form of lesions with incidence of 0.06% in general population and higher prevalence in women (female-to-male ratio 2.3:1). Adrenal endothelial cysts are the most common form of adrenal cysts subtypes (45%) and they usually present with abdominal or flank pain, or nonspecific symptoms (1). Adrenocortical carcinomas are a rare condition as well, with an incidence of 1-2 per million per year. The typical clinical presentation may include symptoms of glucocorticoid excess and systemic symptoms such as weight loss, anorexia, leukocytosis, and fever (3).

We describe a case of a 51-year-old female with poorly controlled hypothyroidism. She presented to endocrinology clinic with a history of fever for three months. The clinical evaluation of fever of unknown origin was unremarkable. A CT scan demonstrated a 3.6X2.6 cm heterogenic mass in the left adrenal . Endocrine blood tests revealed no abnormalities besides overnight dexamethasone (1mg) suppression test that demonstrated partial suppression of cortisol levels (126 nmol/L). As malignancy was suspected, the patient was referred to surgery and the adrenal was removed laparoscopically. Surprisingly, histology confirmed endothelial/vascular cyst. During multiple follow-up visits over a period of 18 months, the fever has completely resolved. This demonstrates the first known case of endothelial/vascular adrenal cyst presenting with persistent fever.

Fatty Acid Binding Protein 4 (FABP4) Secreted From Visceral Adipose Tissue and Glucose Production in Gestational Diabetes Mellitus (GDM)

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GDM is characterized by hyperglycemia and insulin resistance that develops during pregnancy. Altered secretion of adipokines that modulate insulin action during pregnancy is of great importance in GDM pathogenesis. FABP4 is an adipokine with an important role in promoting insulin resistance in various animal models. In humans, FABP4 was suggested to regulate systemic metabolism. Although elevated levels of circulating FABP4 were demonstrated in GDM, its differential contribution to GDM pathophysiology is unclear.

In this study, we aimed to determine the tissue source of elevated circulating FABP4 levels and to assess FABP4 differential contribution in promoting hepatic glucose production in GDM.

We included 71 pregnant women defined as normal glucose tolerant (NGT) and 31 diagnosed with GDM. Maternal level of FABP4 before delivery was measured using ELISA. FABP4 circulating levels were increased in GDM compared to NGT (14.1 IQR: 11.5-21.4 ng/ml vs.10.3 IQR: 6.6-12.4 ng/ml, respectively, p=0.0014). A rapid post-partum decline in FABP4 levels was observed. Using biopsies of placenta, sub-cutaneous (sWAT) and visceral (vWAT) adipose tissues, we observed that FABP4 is secreted from these tissues during pregnancy. FABP4 secretion from vWAT of GDM women was~2 fold higher than that of NGT women. Depletion of FABP4 from vWAT conditioned media of NGT or GDM women using monoclonal antibodies, significantly suppressed glucose production in primary hepatocytes by~20% and~36%, respectively (p0.05).

Taken together, our data highlights the importance of FABP4 in the pathophysiology of enhanced hepatic glucose production in GDM.

Characteristics and Long –Term Outcomes of Patients Hospitalized for Diabetic Ketoacidosis

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Background: Diabetic ketoacidosis (DKA) is an acute metabolic complication characterized by hyperglycemia, ketones in blood or urine, and acidosis.

Objective: Assess the characteristics of patients hospitalized for DKA, identify triggers for DKA and evaluate the long-term effects of DKA on glycemic control, complications of diabetes, re-hospitalizations and mortality.

Methods: Historical prospectively collected data of patients hospitalized to medical wards for DKA between 2011 and 2017. Data regarding comorbidities, mortality, triggers and re-hospitalizations for DKA were also collected.

Results: The cohort consisted of 160 patients (mean age 38±18 years, 43% male).

One fifth of them (34 patients, 21%) were newly diagnosed with diabetes, and DKA was their first presentation of the disease. Among the 126 patients with pre-existing diabetes, the common identified triggers for DKA were poor compliance to treatment (22%) and infectious diseases (18%). During over 7 years of follow-up, mortality rate was 9% (15 patients), and re-hospitalization for DKA rate was 31% (50 patients). Risk factors for re-hospitalization for DKA included young age (OR=1.02, 95% CI, 1.00-1.04), pre-existing diabetes compared to DKA as the first presentation (OR=5.4, 95% CI, 1.7-18), and poorer glycemic control before initial hospitalization (10.5±2.5% vs. 9.4±2.2%; OR=0.8, 95% CI (0.68-0.96)) and after discharge (10.3±2.4% vs. 9.0±1.9%; OR=0.73, 95% CI (0.61-0.87)). Laboratory tests during the initial hospitalization, smoking, alcohol, or comorbidities did not increase the risk for re-hospitalization for DKA.

Conclusions: The risk for readmission for DKA is higher for young patients with long duration of diabetes, poor compliance of insulin treatment and poorly controlled diabetes

Somatostatin Not Only Inhibits GH, but Also Affects LH and FSH Secretion in Tilapia

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Somatostatin (SRIF) is a 14-amino acid peptide produced in the hypothalamus of vertebrates, including fish. It regulates many physiological processes such as growth development. Negative control of GH in vivo and in vitro was characterized on several species of fish.
Therefore, somatostatin inactivity may lead to an increase in GH secretion levels. Surprisingly, although very important, the SST/SST-R system in tilapia was not characterized until now. The somatostatin system in tilapia possess two and five receptors. RNA-seq that was conducted on LH and FSH cell populations in tilapia pituitary discovered 4 types of SST-Rs: sstr2, sstr3, sstr5 and sstr5x3. In vitro assays using COS7 cell line transfected with specific SST-Rs together with a reporter plasmid CRE-luc, demonstrated an effect on cAMP levels. Signal transduction analysis demonstrated that SST agonist decreased the cAMP/PKA pathway, while an opposite effect was found when SST antagonist was used.
To understand the physiological effects of somatostatin on gonadotropin and GH release, we examined the effect of ip injection (100 µg/kg BW) of somatostatin agonist and antagonist on plasma FSH, LH and GH levels.
SST agonist decreased GH and FSH levels in the plasma 2 hours post injection and remain low during the whole experiment.
On the other hand, SST antagonist increased LH and FSH levels 2 hours post injection and while FSH levels remained high during the entire experiment, LH levels went back to basal levels afterwards.
Our results suggest – for the first time in fish – an effect of SST on gonadotropin release.

Prevalence of Impulse Control Disorders in Patients with Pituitary Adenomas Treated with Dopamine Agonists

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Background: Dopamine Agonists (DA) are the first line treatment for prolactin secreting pituitary tumors. DA may also be used for the prevention of post-surgical residual Tumor growth in non-functioning pituitary adenomas (NFPA).
Lately, an increased prevalence of impulse control disorders (ICD) has been described during treatment of prolactinomas with DA.

Aim: To assess the prevalence of ICD in patients with prolactinomas and NFPA's treated with DA compared to patients treated for other medical conditions.

Methods: A validated questionnaire for the diagnosis of ICD was randomly distributed to patients (n=198) arriving for routine visits in our department. 95 patients filled the questionnaires, of which 84 were used for the final statistical analysis.

Results: There were 19 patients with NFA and 12 with prolactinoma, of which nine and ten respectively were under DA treatment. The remaining patients were being treated at the endocrine institute for other medical reasons. Cabergoline-treated patients were younger (55.53 vs. 58.18 years; P = 0.009) and less educated (13.05vs. 14.98years of school; P = 0.009) compared to the control group. 7/19 DA-treated patients reported the presence of ICD compared to 3/65 patients in the control group (36.8% versus 4.6%, P = 0.001).

Conclusion: The incidence of impulse control disorders is significantly higher in patients with pituitary adenomas treated with DA, in comparison with untreated patients or to subjects with other chronic conditions.

Carotenoids and Polyphenols Improve Bone Health Parameters in Human Osteoclasts, Osteoblasts and in a 3D Model of Bone

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In normal Bone, there is constant construction and destruction of bone matrix called bone remodeling. Bone is reabsorbed by Osteoclasts, after which new bone is deposited by osteoblasts.
During Osteoporosis there is excessive bone resorption and inadequate formation of new bone leading to thinning of the bone matrix.
Several clinical and Epidemiological studies show that some Phytonutrients have beneficial effect in Osteoporosis.
The aim of the current study was to examine the effect of various phytonutrients on Osteoblasts Osteoclasts and determine whether combinations of Dietary derived compounds improve parameters of bone Health and to examine the effect of these compounds on 3D model of mineralized bone that we established.
We used Human primary Osteoblasts and examined Alkaline phosphatase levels as a marker for Osteoblasts activity.
Treatment of Osteoblasts during Osteogenic differentiation with Carnosic acid, Curcumin, Lutein or Lycopene led to increased ALP levels, this compounds also increased runt-related transcription factor 2 (Runx2) protein levels in Osteoblasts that examined by W.B.
Osteoclast differentiation was studied in monocytes isolated from Human Blood and treated with M-CSF and RANKL by measuring Tartrate Resistant Acid Phosphatase and by Western blotting and Real Time PCR.
Carnosic acid, curcumin lutein and lycopene and their Combinations inhibit Human Osteoclast differentiation.

Similar effects were seen in a 3D model of mineralized Bone containing Osteoblasts and Osteoclasts.
Our findings suggest that carotenoids and Polyphenols inhibit Osteoclast differentiation and induce Osteoblast differentiation.
We posit that the outcome of our study will be useful for reducing the health burden of Osteoporosis**.**

Phaeochromocytoma-Paraganglioma (PPGL): Post-Operative Hypotension is a vanishing Phenomenon

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Background: Hemodynamic instability in PPGL patients, Intra and Post-Operative periods is challenging. Persistent postoperative Hypotension a serious complication, occurring in 30-60% of patients.
Aim of study was to evaluate efficacy and safety of current preoperative protocol used in our institute.

Methods: Retrospective review. Rate of Hemodynamic instability,relation to efficiency of preoperative Pharmacological preparation in PPGL patients.

Results: 33 subjects had adrenal and 6 extra-adrenal tumors.
F/M 19/20; Age 50.4±16.5 years. Tumor size 3.9±2.2cm. Metanephrine, Normetanephrine levels were 5 and 10 fold the upper limit of normal range respectively.
Patients were treated with α-blockade, phenoxybenzamine-17; 60±38mg/day; doxazosin-22; 9.6±6.1mg/day, along with β-blockade, high sodium diet and IV Saline 0.9%.
Length of preoperative preparation period 3.4±2weeks.
Within the first 24-48 hours from surgery no episodes of Hypotension.

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

Low Risk for all-cause Mortality among Patients with Lung Neuroendocrine Tumor Co-diagnosed with Pituitary Adenomas

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Introduction: Lung Neuroendocrine Tumors (LNET) and Pituitary Adenomas (PA) may develop sporadically, or as part of a hereditary syndrome, such as multiple endocrine neoplasia type 1 (MEN1). MEN1 clinical diagnosis is established in the presence of two of the MEN1 triad: parathyroid adenoma, Enteropancreatic Neuroendocrine Neoplasm and PA, excluding LNET as a diagnostic criterion.
We characterize a unique population of patients with both LNET and PA.

Methods: A retrospective study based on the Surveillance, Epidemiology and End Results database. Patients diagnosed with both LNET and PA or with LNET only were included. Demographic characteristics and risk for all-cause mortality were compared in univariate and multivariable analyses.

Results: 1077 patients had LNET (61.6% women) and 27 (2.5%) were also diagnosed with PA (37.0% women, p=0.02), higher than the general population prevalence (77-115/100,000, z-test, p=0.0042).
In most patients (81.5%) PA was diagnosed earlier (mean 2.39±3.53 years).
Cases had a higher rate of distant metastases (48.1% vs. 15.2%, respectively, p0.001), higher mortality rate (log-rank test, p=0.00045) with a time to reaching median of 73y (95% confidence interval [CI] 69-79) vs. 78y (95% CI 79-82) respectively.
In a multivariable analysis, cases had higher risk for overall mortality (hazard ratio 2.738, 95% CI 1.659-4.519, p0.001). Male gender, distant Metastasis and low LNET differentiation were Independently associated with poor prognosis.

Discussion: Patients with LNET had a higher PA prevalence compared with the general population, suggesting a genetic predisposition. This is further supported by the higher mortality-risk among patients with both PA and LNET vs. LNET alone.

Blood Pressure Dynamics after Pubertal Suppression with Gonadotropin Releasing Hormone Analogs Followed by Testosterone Treatment in Transgender Male Adolescents

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Aim: The effects of gonadotropin-releasing-hormone analog (GnRHa) treatment on the cardiovascular system of youth with gender dysphoria remain an issue of concern. This retrospective, observational study analyzed blood pressure (BP) changes in transgender male adolescents treated with GnRHa and after the addition of gender-affirming testosterone treatment.

Methods: All transgender male adolescents who had received GnRHa for ≥2 months in a pediatric gender dysphoria clinic were recruited. Outcome measures included systolic (SBP) and diastolic BP (DBP) percentiles before and after GnRHa initiation and after the addition of testosterone treatment.

Results: Fifteen transgender males (mean age at baseline 14.4 ± 1.0 years) received GnRHa for 3 ± 1 months. Testosterone treatment was added in nine subjects at age 15.5 ± 0.9 years. DBP percentiles increased significantly after GnRHa treatment (from 55.9% ± 26.4 to 73.6% ± 9.4, p = 0.019). BP levels were within the normal range and did not meet criteria for pediatric hypertension. DBP percentiles decreased significantly after adding testosterone therapy (from 72.8% ± 10.1 to 56.0% ± 17.5, p = 0.033) only after adjusting for the change in body mass index standard deviation score. SBP percentiles did not change significantly throughout treatment. BP percentiles did not correlate significantly with luteinizing hormone, follicle-stimulating hormone and estradiol levels.

Conclusion: Pubertal suppression with GnRHa increased DBP percentiles in transgender male adolescents, and subsequent pubertal induction with gender-affirming testosterone treatment restored them. The effects of BP dynamics on the cardiovascular consequences in gender dysphoric adolescents warrant further study.

Adipocyte Connexin-43 as a Mediator of Adipose Tissue Dysfunction in Obesity

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Obesity is a leading Global Health concern and a Major Risk Factor for type-2 Diabetes.
Thus, identifying mechanism(s) linking Obesity to insulin resistance and impaired Metabolic Homeostasis is of great importance.
Chronicl Low-Grade Inflammation of the Adipose Tissue (AT) and Cellular Dysfunction of the Obese Adipocytes have been shown as an important Pathophysiological link between Obesity and the Development of systemic Insulin resistance, in mechanisms that are not fully understood.
Increased gap Junction activity, primarily composed of Connexin-(Cx)43, has been shown to play a pivotal role in the response of various Tissues to chronic Stress conditions.
In a diet-induced Obesity mouse model we demonstrated an increase in Cx43 expression in the intact AT, which could be primarily attributed to increased Cx43 expression in Adipocytes.
In high fat diet-fed Adipocyte-specific Cx43 knock-out mice (AdCx43KO), we observed increased infiltration of Macrophages to the AT as compared to wild-type mice.
Yet, despite increased immune cell infiltration, the AT of AdCx43KO mice presented with a significant decrease in expression of inflammatory markers, accompanied by smaller mean adipocyte size, characteristic of Higher Insulin sensitivity.
Indeed, AdCx43KO mice demonstrated lower fasting Glucose levels and improved Insulin sensitivity.

Our results suggest that in Obesity, adipocyte Cx43 plays an Immunomodulatory role in the AT, contributing to the Development of AT dysfunction and consequential Impairment of systemic Metabolic Homeostasis. Our findings may imply Cx43 as a novel therapeutic target for obesity-associated Metabolic Abnormalities.

The Prevalence of Anti-Parietal Cell and Tissue-Transglutaminase Antibodies in Patients with Autoimmune Thyroid Disease

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Background: The prevalence of Autoimmune Gastritis (AG) and Celiac Disease (CD) in Autoimmune Thyroid Disease (AITD) have been estimated at 20-25% and 2-5%, respectively.
Although both conditions are associated with significant morbidity, no international guideline recommends screening.

Objective: To assess the prevalence of Parietal Cell Antibodies (PC-Ab) and Tissue-Transglutaminase Antibodies (tTg-Ab) in AITD patients.

Methods: Epidemiological and clinical data of AITD patients who presented to our clinic between 11/05/2015-13/06/2019 were reviewed.

Results: Three-hundred and seventy-three AITD patients matched inclusion criteria; 326 (87.4%) were females; 61(16.4%) Arab.
One-hundred and ninety-nine (53.4%) were Hypothyroid, 124 (33.2%) Hyperthyroid, 8 (2.1%) with mixed disease and 28 (7.5%) Euthyroid. tTg-Ab was assessed in 237 (63.5%)patients; PC-Ab in 126(33.8%).
PC-Ab screening performance was not associated with gender, ethnicity, clinical thyroid disease or TPO status; there was a trend towards lower vitamin B12 levels in patients screened for PC-Ab.
Of those tested, PC-Ab was positive in 33/126 (26.2%).
There was no significant correlation between PC-Ab positivity and Gender, Ethnicity, Clinical Thyroid Disease, TPO status or vitamin B12 level.
tTg-Ab were positive in 8/237 patients (3.4%); 2 additional patients had known CD.
Nine patients were female; 2 had concurrent PC-Ab antibodies.

Conclusion: The frequency of tTg and PC-Ab in this study is concordant with prior studies` results.
However, screening rates were relatively low, despite our recommendations, potentially leading to under-diagnosis. The increased prevalence of CD and AG in AITD across multiple studies, together with their important morbidities and treatment implications, advocates for a role for screening in AITD.

The OsteoSee System Measurements, Based On parametric Electrical Impedance Tomography (pEIT), Correlate with Dual X-Ray Absorptiometry Results for the Diagnosis of Osteoporosis.

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Introduction: The OsteoSee @Clinic is a novel portable and user-friendly system, which uses parametric Electrical Impedance Tomography (pEIT), being developed for the screening of osteoporosis

Aim: To compare OsteoSee @Clinic to DXA.

Methods and Subjects: Subjects who underwent a routine DXA scan were scanned with the OsteoSee @Clinic system (OsteoSee Ltd., Israel) using 5 electrodes placed around the left distal forearm and pelvis.

Results: Correlations were examined between pEIT-index of the pelvis versus DXA total hip BMD. Sensitivity and specificity were calculated according to the DXA total hip T-score diagnosis. An analysis of 182 subjects (35 healthy, 115 osteopenia, 32 osteoporosis) scanned on the wrist showed an R-value of 0.795 (p-value 0.001) between the pEIT-wrist index and DXA results.
From the ROC plot, we obtained a sensitivity of 84% and specificity of 71% to diagnose Osteoporotic vs osteopenic & normal subjects, and a sensitivity of 82% and specificity of 86% for identifying osteopenic & osteoporotic vs normal subjects.
An analysis of 98 subjects (17 healthy, 66 osteopenic, 15 osteoporosis) scanned on the pelvis showed an R-value of 0.740 (p-value 0.001) between the pEIT-pelvis index and BMD.
From the ROC plot, we obtained a sensitivity of 80% and specificity of 81% to diagnose Osteoporotic vs Osteopenic & normal subjects, a sensitivity of 70% and specificity of 76% for identifying Osteopenic & Osteoporotic vs normal subjects.

Conclusions: The OsteoSee @Clinic system results correlate well with DXA measurements. Sensitivity and specificity values indicate it can provide screening and diagnosis of Osteoporosis.

Long-term Response to Cabergoline Treatment in Men with Macroprolactinoma is Independent of Tumor Size

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Objective: To study the outcome of men with macroprolactinoma following cabergoline treatment based on tumor size.

Methods: The study included 96 men, aged 16–84 years (mean 47.3 years) treated with cabergoline (weekly cabergoline dose, 0.5-10 mg) at a single center, for a mean follow-up of 7.5 years. The cohort was divided into 3 groups according to baseline adenoma diameter: group A, adenomas of 10-19 mm (n=36), group B, 20-39 mm (n=43), and group C, giant prolactinomas ≥40 mm (n=17). Patients were followed with sellar MRI, visual fields, and hormone measurements.

Results: Mean prolactinoma diameter was 15.0, 28.1 and 49.8 mm in group A, B and C, respectively, decreasing following treatment to 7.6, 13.6 and 16.6 mm (P0.01).

Visual defect was depicted in 4 (11%), 14 (33%) and 9 (56%) patients (p=0.03) in group A, B and C, respectively. Improvement was achieved in 4/4, 13/14 and 9/9 men.

Mean baseline prolactin was 685, 2,134 and 24,316 ng/mL (P0.01) in group A, B and C, respectively. Prolactin suppression to below 3 x ULN achieved in 34 (94%; mean weekly cabergoline dose, 1.2 mg), 35 (81%; cabergoline dose, 2.0 mg) and 14 (82%; cabergoline dose, 2.8 mg) men (p=0.21) in the different groups.

Low baseline testosterone was discovered in 26 (72%), 40 (93%) and 17 (100%) patients (p0.01) in group A, B and C. Hypogonadism following treatment persisted in 2 (6%), 5 (11%) and 2 (12%) men, respectively (p=0.61).

Conclusion: Cabergoline is effective in most men with macroprolactinoma, regardless of initial tumor size.

The Challenges of Treating Glucokinase MODY During Pregnancy

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Introduction: Glucokinase–Maturity-onset Diabetes of the young (GCK-MODY) is inherited Diabetes caused by mutations in the Glucokinase gene.
Management through Pregnancy differs substantially from other types of Diabetes but no clear guidelines exist.
Pregnancy outcomes depend upon fetal mutational status, which remains unknown in most cases.
Most support fetal growth follow-up on serial ultrasounds and if accelerated, suggesting a non-carrier fetus, treatment is indicated.
Fetal growth assessments are influenced by maternal weight pre- and during pregnancy.
Overlapping "Gestational-Induced Hyperglycemia" further complicates decision making.

Methods: We describe here three women with genetically confirmed GCK- MODY who were followed at the integrated Diabetes-Maternal-Fetal Medicine clinic at Kaplan Medical Center.
Fetal mutational status was known for two.

Results: One case was complicated by the presence of positive Anti-Insulin Antibody.
The second had significant Hyperglycemia early on and her fetus was a non-carrier.
The third woman presented accelerated fetal growth although her fetus did carry the mutation.
Insulin treatment was eventually administrated to all regardless of fetal mutational status.
None of the newborns presented Macrosomia or Hypoglycemia.

Conclusions: These data imply that identifying maternal and fetal mutational status is not sufficient to guide treatment and other variables complicate treatment decisions.
The suggested algorithm of serial fetal growth sonography does not take into consideration other factors influencing fetal weight gain nor the fact that glucose intolerance in the third trimester might superimpose. In addition, no consensus exists for glucose targets during GKC MODY pregnancy.
More data are needed to guide the management of these women.

Insulin Requirement through-out Pregnancy in Women with Type 1 Diabetes

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Introduction: The aim of this study was to evaluate the change of total, basal and bolus insulin requirements throughout pregnancy in patients with T1DM treated with insulin pump.

Methods: The study included all consecutive T1DM women treated with insulin pump and monitored in a single tertiary care center. Clinical and demographic variables as well as data regarding glucose control and insulin requirements were prospectively recorded. A one-way repeated measured of variance (ANOVA) was conducted to compare the effect of gestational age on mean total, basal and bolus insulin (units/Kg body weight) requirements. Subsequently, a similar analysis was conducted in two subgroups: normal weight and over-weight/obese patients

Results: Data regarding insulin requirements of 101 pregnancies, in 6-week intervals throughout pregnancy were included in the analyses. There was a statistically significant increase in mean total, basal and bolus insulin requirements with increasing gestation (Wilks' Lambda 0.16, 0.24 and 0.26 respectively, p 0.001 for all comparisons) (figure 1).

Post hoc tests using the Bonferroni correction revealed that total, basal and bolus insulin requirements were higher during the third trimester compared to both first and second trimesters. Similar findings were found when the analysis included only normal weight or overweight obese patients.

Conclusions: In women with T1DM treated with insulin pump mean total, basal and bolus insulin (units/Kg body weight) requirements increased as and function of gestation age regardless of BMI category.

Gestational Weight Gain does-not Affect Insulin Requirement During Pregnancy in Women with Type 1 Diabetes

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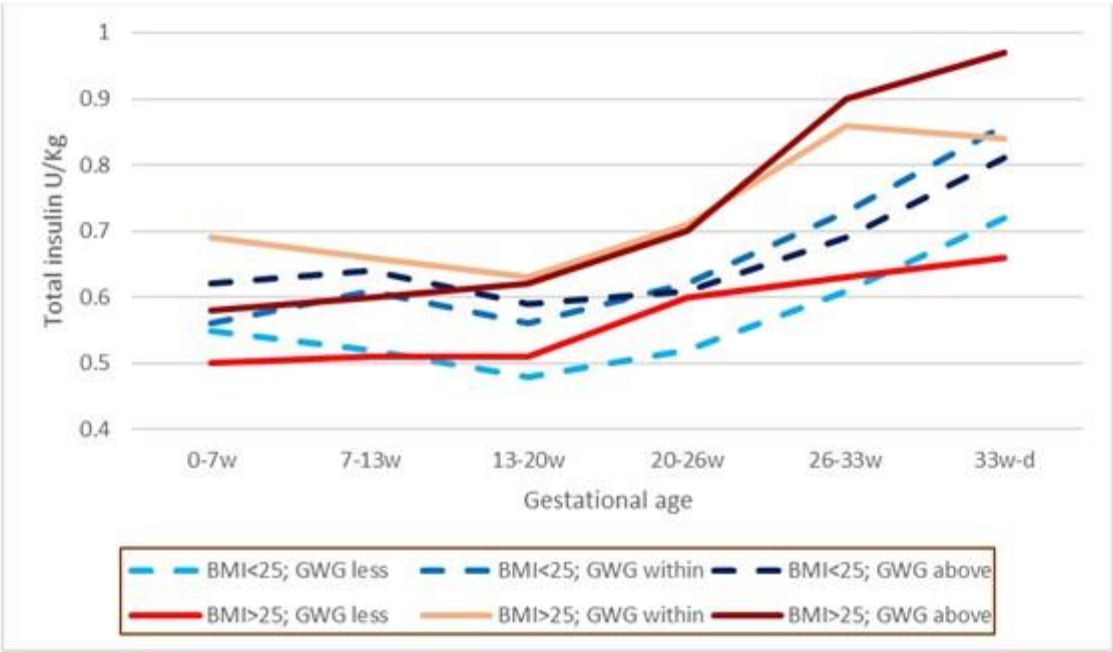
Introduction & Aim: To determine the effect of Gestational weight gain (GWG) according to BMI categories on insulin requirements in patients with T1DM treated with insulin pump**.**

Methods: The study included all consecutive T1DM women treated with insulin pump and monitored in a single tertiary center. Clinical and demographic variables as well as data regarding glucose control and insulin requirements were prospectively recorded. A three-way ANOVA was conducted to examine the effect of gestational age on insulin requirements (units/kg body weight) in patient according to GWG category (Institute of Medicine weight gain recommendations for pregnancy) and BMI categories dichotomized to normal weight (BMI25) or overweight/obese patients (BMI25).

Results: This analysis pertains to 96 pregnancies. There were no statistically significant differences in glucose control indices and pregnancy outcomes according to either GWG or BMI categories (figure).There was no statistically significant interaction between the effects of time on GWG or on BMI category nor between GWG and BMI category.Mean total, basal and bolus insulin requirements (units/kg) increased significantly between time points (Wilks' Lambda 0.15, 0.26 and 0.27 respectively, p Post hoc tests using the Bonferroni correction revealed that total, basal and bolus insulin requirements were higher during the third trimester compared to both first and second trimesters regardless of GWG or BMI category.

Conclusion: In women with T1DM treated with insulin pump insulin requirements during pregnancy (units/kg) increased as a function of gestation age regardless of GWG or BMI category.

Figure: Total insulin requirements (units/kg) throughout pregnancy according to Gestational Weight Gain and BMI category



*Gestational weight gain (GWG) categories: less, within and above IOM recommended GWG.

*w=week; d=delivery; BMI=body mass index

Unannounced Meal Challenges in a Protected Free-Living Environment using the Medtronic Advanced Hybrid Closed Loop System

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Background and Aims: Advanced Hybrid closed loop (AHCL) algorithm combines automated basal rate with additional enhancement when a rise in Glucose level is detected.
This study assessed the effectiveness and safety of AHCL with no Pre-Meal bolus for graded Carbohydrate content meals.

Methods: Four participants were followed for 4 days in a protected free living environment, while consuming 12 Pre-Defined meals consisting of 40, 60 and 80 grams of Carbohydrates each day.
Comparison of overall Glycemia and post prandial Glucose excursions following announced (5 meals) vs unannounced (6 meals) were conducted.

Results: preliminary results of 4 adult participants show that overall Glycemia during the unannounced meal phase demonstrated a 73.2% (±9.6) TIR 70-180 with no Hypoglycemia 70 mg/dL.
These results were associated with reduction in total daily dose and minimal requirements for Glucose salvage. The peak Glucose levels of unannounced meals did not differ between the 40, 60 and 80 gram Carbohydrate-containing meals, although there was a trend towards an increased area under the post-meal Glucose curve with higher Carbohydrate content of meals.

Conclusion: Medtronic AHCL system is programmed for meal announcement.
Nevertheless, when meals containing 80 gram of Carbohydrates are consumed without meal announcement, the system is able to provide safe Glycemic control with over 70% of TIR.

Table 1. Data of 2 consecutive days with only unannounced meals in a protected free-living environment with the Medtronic Advanced Hybrid Closed Loop system.

Mean SG, mg/dL	147.5 (14.6)
70-180 mg/dL, %	72.2 (9.6)
<70 mg/dL, %	0 (0)
<54 mg/dL, %	0 (0)
>180 mg/dL, %	26.8 (9.6)
>250 mg/dL, %	1.7 (2.4)

Data presented as mean, (SD).

OsteOosee: A Novel Tabletop Device for Screening and Diagnosing Osteoporosis

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Objective: Osteoporosis is underdiagnosed and undertreated, in part due to various barriers to DXA screening. OsteoSee system is a novel tool for BMD measurement, based on bio-impedance technology.

The aim of the present study was to compare BMD results by OsteoSee @Clinic (OS@C) to those by DXA.

Materials: OS@C uses parametric Electrical Impedance Tomography (pEIT), to measure spatial electrical conductivity distribution within the organ (Figure). Five electrodes around the wrist serve as current flow origin and electric potential meter and bone dielectric properties can be calculated. The result is classified similarly to BMD measurement byDXA.

Methods: Subjects referred for a routine DXA scan participated in the study and were measured by OS@C.

We used a multidimensional discriminant analysis, a machine-learning algorithm, to calculate 2x2 and 3x3 confusion matrices that provided the accuracy of the OS@C system relative to the DXA.

The final diagnosis (normal, osteopenia, osteoporosis) based on the DXA scan was used for comparison.

Results: Results of 87 subjects were analyzed. OS@C identified patients with osteoporosis/osteopenia&osteoporosis with sensitivity of 82% and 91%, respectively. The congruence of the system to DXA classification for normal, osteopenia and osteoporosis was 91%, 76% and 74%, respectively.

Conclusions: OS@C system results correlate well with the gold standard DXA-based classification. The point-of-care tabletop system enables BMD measurement within a few minutes, does not require special training, spares exposure to ionizing radiation and can be used for screening and diagnosis at the primary or secondary care facilities.

Disclosure: The study was funded by OsteoSee Ltd., Israel

Predicting BMD Result: Validation of Osteoporosis Risk Indices in Israeli Population

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Background: Bone mineral density (BMD) screening is recommended for men and women above age-based cutoffs but is underused.
Presence of risk factors for fracture lowers the proposed screening age. Several risk indices (OST, ORAI, OSIRIS and SCORE) were developed to identify subjects with high probability for Osteoporotic-range BMD, testing of whom should be further reinforced.

Aim: Validation of BMD risk indices in Israeli population.

Design: Retrospective cross-sectional study.

Methods: Institutional BMD database was utilized.
Information on risk factors was derived from routine pre-BMD questionnaires. Patients receiving bone-deteriorating or osteoporosis medications were excluded. Accuracy of indices in predicting T-score = -2.5 was calculated.

Results: A total of 4,492 patients were eligible for analysis. The Osteoporosis Self-Assessment Tool (OST) displayed sensitivity and specificity of 84% and 41% vs. 68% and 54% with negative predictive value (NPV) of 85% and 87% in women and men, respectively.
ORAI, OSIRIS and SCORE performed with sensitivity of 76%-94%, and specificity of 22%-55% in women.

In a subgroup of younger patients (50-60 years), OST displayed sensitivity and specificity of 67% and 55% vs. 33% and 86%, with NPV of 84% and 85% in women and men, respectively. ORAI, OSIRIS and SCORE performed with sensitivity of 53%-88%, and specificity of 31%-75% in women.

Discussion: Simple risk indices for prediction of BMD in the osteoporotic range have high sensitivity in our population, consistent with previous population studies.

Self-applied OST may be a useful tool for pre-test indication stratification due to its high negative predictive value at younger age.

The Impact of Flash Glucose Monitoring Technology on Glycemic Control and Healthcare Services Consumption in Patients with Type 1 Diabetes - A Nationwide Cohort Study

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Introduction: Good glycemic control in patients with Type-1 diabetes (T1D) mandates frequent glucose monitoring and insulin dose adjustment. Flash glucose monitoring (FGM) technology has been recently included in the Israel National Health-Basket for adults with T1D.

Aim: To evaluate the impact of FGM on glycemic control and use of healthcare services.

Methods: This non-interventional retrospective study included Clalit Health Services (CHS) members aged ≥18 years with T1D who first purchased a FGM sensor between 1.1.2018-31.12.2018 (index-date). Included subjects were CHS members for at least 6 months prior to and following index-date, and had purchased in average at least one sensor/month. Healthcare services consumption during 6 months prior to index-date was compared to utilization during follow-up period.

Results: Study included 3,490 patients followed for a median of 14 months (IQR 11-15) following FGM purchase. Number of internal-medicine hospitalizations, admissions for diabetic ketoacidosis and/or severe hypoglycemia, visits to primary-care as well as visits to diabetes or endocrine specialty clinics significantly declined from baseline to follow-up (p. Mean HbA1c declined from 8.1%±1.46 at baseline to 7.9% ±1.31 (first measurement at ≥3 months, p0.01). An HbA1C decrease of ≥0.5 was observed in 683/2,682 (25.5%) of patients, and was independently associated with younger age and higher baseline HbA1c.

Conclusions: FGM initiation was associated with improved glycemic control and reduced health services consumption.

Denosumab-induced Hypocalcemia: Does Gender Play a Role?

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Introduction: The recognition that disease presentation, treatment and outcomes may differ between men and women has become established. We have recently reported a-7.4% rate of denosumab-associated hypocalcemia in community-dwelling osteoporotic patients.

Aim: To investigate the role of gender in this complication.

Methods: A retrospective analysis of medical records (2010-2018) from a large HMO. An albumin-adjusted serum calcium concentration ≤8.5mg/mL was defined as hypocalcemia.

Results: A total of 1871 women and 134 men were included. Men were older (median 81 vs. 77 years, p=0.004), more likely to receive denosumab as first-line treatment (22% vs. 6%, p0.001), were treated less with calcium supplements (42% vs. 53%, p=0.024) and had a lower median eGFR level compared to women (66.1 vs. 79.9 mL/min/1.73m2, p0.001). Denosumab-associated hypocalcemia developed in 133 women (7.1%) and in 16 men (11.9%) (p=0.04). The strongest predictors of hypocalcemia in women were pretreatment levels of albumin-adjusted serum calcium (OR 0.08, 95% CI [0.04, 0.14]) and creatinine (OR 2.43, 95% CI [1.45, 4.05]). There were no predictors for hypocalcemia in men, probably due to the small cohort. Gender was not a predictor for hypocalcemia after propensity matching of 126 men versus 126 women.

Conclusion: Contrary to previous reports, male gender per se is not a risk factor for denosumab-associated hypocalcemia. Despite increasing recognition of male osteoporosis, there was a considerable difference in the number of treated men and women. Men who received denosumab were significantly older with lower GFR, therefore are probably more prone to develop hypocalcemia.

Temporal Trends in Incidence, Evaluation and Management of Neuroendocrine Neoplasms of the Appendix- 14 Years` Experience

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Background: Data regarding trends in incidence and prognosis of Appendiceal Neuroendocrine Neoplasms (ANEN) is limited.

Aims: To evaluate temporal trends in ANEN incidence, evaluation and management over a 14- year period.

Methods: Appendectomy pathology reports from a single tertiary center were reviewed. Data of ANEN patients were collected from electronic patient files.

Results: Between January 2005 and December 2018, 8,327 appendectomies were performed. A total of 57 ANENs were diagnosed (age 31.7±17 years; 70.2% females; 17.5% of Arab ethnicity; and 22.8% 18 years of age). The cohort was subdivided according to year of diagnosis into Period A (2005-2011) and Period B (2012-2018).

No differences were found in ANEN incidence (0.68% and 0.62%, respectively, p=0.104) or epidemiologic characteristics between periods. Pathologic features were similar in the two subgroups, although pathology reports were more comprehensive and applicable to international guidelines in Period B. Follow-up in dedicated clinics and use of specific imaging and biochemical studies were also more prevalent in Period B. Fifteen patients underwent right hemicolectomy (8 in period A, 7 in period B, p=0.925). Pathologic features of these 2 subgroups were similar. All patients remained alive for the duration of follow up (10.8±1.7 years in Period A and 3.5±1.9 years in Period B, p0.001).

Conclusions: Over a 14-year period, no distinct temporal changes in epidemiological, clinical or pathological features of ANENs were noted. Although after 2011 the clinico-pathological evaluation was more detailed and elaborated, there was no change in hemicolectomy.

Atypical Femoral Fractures and Bisphosphonates Exposure among Patients Participating in a Fracture Liaison Service

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Bisphosphonates (BP) stand as a pillar stone for Osteoporosis (OP) treatment.
However, prolonged treatment is associated with atypical femoral fractures (AFFs).
It was our aim to characterize AFFs among the Fracture Liaison Service (FSL) cohort of a Tertiary Medical Center.
From July 2014 to November 2018, patients over age 50 admitted and operated for Osteoporotic Hip fracture were included in the FLS. AFFs were defined using the revised American Society for Bone and Mineral Research (ASBMR) criteria.
Patients with typical hip fractures and those with AFF were compared according to demographic, clinical, biochemical data, and exposure to BPs prior to the index fracture.

During the study period 1117 patients were included in the FLS.
Full clinical and radiological data were available for 989 patients.
Following evaluation, 31 patients (3.13%) were judged to fulfill the criteria for an AFF.
Patients with AFF were younger than patients with typical per-trochanteric hip fracture (72.35 ± 10.3 vs. 80.19 ± 9.6, p0.001), and had lower Charlson's Comorbidity Index (mean±SD, 2.87±3.74 vs. 5.52±4.33, p=0.008). Five years BPs treatment rates were higher among patients with AFF (51.6% vs. 16.7%, p0.001). Multivariate Analysis corrected for age and gender showed a strong association between AFF occurrence and BPs treatment, odds ratio= 5.50 (95% CI, 2.45 to 12.38).

In our sample of patients with osteoporotic hip fractures treated by the FLS, 3.14% presented AFF.
Our results support the association between BPs treatment and AFF, especially when this treatment is prolonged.

Sodium Glucose Cotransporter 2 Inhibitors in Acromegalic Patients with Diabetes

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Background: Sodium glucose cotransporter (SGLT)-2 inhibitors represent a novel class in type 2 diabetes mellitus (T2DM) management and despite its positive aspects, this class is rarely recommended for acromegalic patients with diabetes.

Methods: To report first three cases of acromegalic patients with diabetes treated successfully with SGLT-2inhibitors, and to provide a systemic review regarding the characteristics of patients with acromegaly and DKA.

Cases presentation: The first case describes a 41-year-old man diagnosed with diabetes one year before acromegaly diagnosis. He was treated with metformin and basal bolus insulin. Postoperatively, worsening hyperglycemia was observed after switching his treatment to pasireotide LAR due to elevated IGF-1. A weight reduction effect with glycemic control was achieved after empagliflozin treatment. In the second case, we describe a 51-year-old woman diagnosed with acromegaly since 2007. After transsphenoidal resection lanreotide autogel was administrated. IGF-1and GH remained consistently elevated therefore pegvisomant (PEGV) was added and discontinued later due to severe headache. Diabetes developed after switching to PAS-LAR and treated effectively with empagliflozin. The third case describes a 63-year-old man diagnosed with T2DM since 2007. Acromegaly due to microadenoma was diagnosed recently. Prior to transsphenoidal adenoma resection, a combination antidiabetic treatment including dapagliflozin was given without any adverse events. Reviewing the literature, DKA was the initial presentation for unrecognized acromegaly.

Conclusions: The use of SGLT-2 inhibitors seems to be safe in patients with diabetes and recognized acromegaly. DKA was the initial presentation in patients with unrecognized acromegaly. SGLT-2inhibitors should be considered for patients with diabetes and controlled acromegaly.

Subacute Thyroiditis: Clinical Presentation and Long-term Follow-up

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Background: Subacute thyroiditis (SAT) is a common inflammatory condition. However, only few studies evaluating SAT were published in recent years with inconsistent diagnostic criteria.

Objective: to evaluate the clinical presentation, course and long-term outcome of isotope scan-confirmed SAT.

Subjects and Methods: A retrospective study of 38 consecutive patients with isotope scan-confirmed SAT, during 2015-2018. All scans were performed at Kaplan Hospital Isotope Department. Patients were contacted to assess long-term follow up.

Results: The female/ male ratio was 1.4:1, mean age was 47±14 in women and 62±12 in men (p=0.002). Almost half of the cases (42%) occurred during summer. The most common symptoms were neck pain (73%), and weakness (60%). Palpitations, weight loss, heat intolerance, sweating, and diarrhea appeared in 50%,42%, 21%, 21% and 7%, respectively. Only half of the patients reported of fever. Mean FT4 level was 41.0 ± 22.2 pmol/L, and FT3 14.0±7.2 pmol/L. Elevated CRP and ESR occurred in the majority (88%). The mean time period between the first clinic visit and performing thyroid function tests was 8±7 days. One third of the patients initially received a diagnosis of upper respiratory tract infection (URI). NSAIDs and steroids were prescribed to 47% and 8% patients, respectively. Long-term follow-up (range 6-42 months) revealed that 25% remained with subclinical or overt hypothyroidism.

Conclusions: These data demonstrate that although SAT is a known common entity, there is still a significant delay in its` diagnosis and in a third of our patients the initial diagnosis was URI. A quarter of patients developed hypothyroidism.