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הכנס המדעי ה-50 של האגודה
הישראלית לאנדוקרינולוגיה

מלון ענבל, ירושלים

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Abstract Book

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The Effect of Over-and-undertreatment of Hypothyroidism on Hospitalization Outcomes of Patients with Decompensated Heart Failure

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Background:
Hypothyroidism has profound effects on cardiac function, however, the effect of over- and undertreatment of hypothyroidism on hospitalization outcomes of patients with acute exacerbation of heart failure (HF) has not been evaluated yet.

Methods:
We conducted retrospective cohort analyses of outcomes among 231 consecutive patients with treated hypothyroidism who were admitted to the internal medicine departments of Shamir Medical Center with HF from 2011 to 2019. Patients were divided into three groups according to their TSH levels. The main outcomes were functional deterioration, in-hospital mortality, and recurrent hospitalization within three months.

Results:
Among 231 patients, 106 were euthyroid, 14 were overtreated, and 111 were undertreated. Patients' mean age was 79.8±9.4 years. In-hospital mortality occurred in 4.7% in euthyroid patients, 14.3% in the overtreated group, and 10.7% in the undertreated group (p= 0.183). Differences in 30- and 90-days mortality or functional deterioration were not significantly different. However, in patients with extreme values of TSH (0.4mIU/L or 10mIU/L), there was a higher 90 days mortality rate (30.4% vs 15.1%, p=0.016), as compared to patients with normal or mildly increased TSH (0.4-10 mIU/L).

Conclusion:
Our results show that mild under- or overtreatment of hypothyroidism did not have a significant detrimental effect on mortality, functional deterioration, or rehospitalization of patients with acute decompensated HF. However, significant over- and undertreatment do cause adverse hospitalization outcomes. Larger cohorts are needed to establish the relationship between treatment targets and hospitalization outcomes of patients who are at risk for decompensation of HF.

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Intravenous Thyroxine Administration to Hospitalized Patients Outside of Approved Indications: A Common, yet Unreported Practice a Single-center Observational Study

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Background:
Intravenous thyroxine (IVT4) is FDA-approved solely for the treatment of myxedema coma (MC). However, it appears IVT4 is not uncommonly administered for unapproved indications. We aimed to characterize a recent cohort of hypothyroid (HT) inpatients who received IVT4, to understand the motives behind treatment, and to assess their outcomes.

Methods:
A retrospective study of all admissions at Tel Aviv-Sourasky Medical Center between 01.01.2017-30.06.2020, during which at least one dose of IVT4 was administered. Demographic, clinical data, and outcomes were retrieved. A MC index (MCI), together with the age-adjusted Charlson co-morbidity index (AACCI), were used to assess the patients' clinical condition. A multivariate analysis was performed to explain the outcome death.

Results:
IVT4 was administered to 104 HT subjects over the course of 110 admissions. MC was confirmed in only 4 (3.6%), 11 subjects received IVT4 for lack of enteral access/malabsorption. Thus, IVT4 was administered for ATA-endorsed indications in only 15/110 (13.6%) of the cases. The most common justification for treatment was perceived profound hypothyroidism (57/110, 51.8%). There were 27 fatalities (24.5%). In a logistic regression, artificial ventilation (aOR 7.69 [CI 2.3-28.3], P=0.0012), and the AACCI (aOR 1.34 [CI1.09-1.73], P=0.012 were the only significant independent predictors of death. Thyroid function tests had no discriminatory power.

Conclusions:
IVT4 was rarely given for ATA-endorsed indications. Although it doesn't appear to be detrimental, a beneficial effect on outcome remains unproven. Death was due the patients' condition, not to hypothyroidism. Controlled prospective trials of IVT4 for indications other than those currently ATA-approved are required.

Can Mild to Moderate Iodine Insufficiency During Pregnancy Alter Thyroid Function? Lessons from Mother-newborn Matching Pairs Cohort

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Background:
Severe iodine deficiency (ID) during pregnancy has substantial hormonal consequences, such as irreversible fetal brain damage. However, data on the potential effects of mild-to-moderate (ID) on thyroid function of pregnant women and their newborns are
scarce and divergent.

Objective:
We investigated the association between iodine status in pregnancy and both maternal and neonatal thyroid function in a region with mild-to-moderate ID.

Methods:
A single-center study, including rigorious observation during pregnancy and birth. Pregnant women's iodine status was evaluated by an iodine food frequency questionnaire, serum thyroglobulin (Tg), urinary iodine concentration (UIC). Neonatal thyrotropin (nTSH) values were measured after birth. Obstetrics and anthropometric data were also collected.

Results:
Among the 178 women (median age 31 years) included in the study, median (interquartile range) estimated dietary iodine intake, Tg and UIC were 179 (94-268) µg/d, 18 (11-33) µg/L, and 60 (41-95) µg/L, respectively. There was a significant inverse association of iodine intake with Tg values among the study population (β=−0.2, F=7.5, p0.01). Women with high free triiodothyronine (FT3) values were significantly more likely to exhibit an estimated iodine intake below the estimated average requirement (160 µg/d, odds ratio [OR]=2.6; 95% confidence interval [CI], 1.1-6.4; p=0.04), less likely to consume iodine-containing supplements (OR=0.3, 95% CI, 0.1-0.8; p=0.01), and deliver a greater proportion of newborns with nTSH ≥20 IU/L (p=0.04).

Conclusions:
Iodine insufficiency during pregnancy in regions with mild ID may be associated with altered maternal thyroid function. The relatively small sample size of the studied population and the possible association with congenital hypthyroidism warrants further investigation.

Long Term Follow-up and Outcomes of Autoimmune Thyroiditis in Childhood

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Background:
Autoimmune thyroiditis (AIT) is the most common cause of acquired hypothyroidism in children. The natural outcome of AIT in childhood has been reported previously, however follow-up duration is generally short and results variable.

Objectives:
To characterize clinical and biochemical findings at presentation of AIT, evaluate long-term outcomes and assess which factors at presentation predict evolution over time.

Study Cohort:
201 children under 18 years of age at presentation (82% female) were enrolled. Subjects were divided into five subgroups according to thyroid stimulating hormone (TSH) level at referral.

Results:
Mean follow-up was 8.1 years (range 0–29 years). At presentation, 34% of patients had overt hypothyroidism, 32% subclinical hypothyroidism (SCH), 16% compensated hypothyroidism, 14% were euthyroid, and 3.7% had Hashitoxicosis. Children with overt hypothyroidism were younger (10.6 vs. 13.2 years) and had higher thyroid peroxidase antibody titers. Fifty patients (25%) had an additional autoimmune disease diagnosed either before or after AIT diagnosis and in 40%, a family history of thyroid disease was present. At the time of the study, levothyroxine (LT4) therapy was required in 26% of children who were euthyroid at presentation, 56% of SCH patients, 83–84% of those with TSH above 10 mIU/L, and 57% of those with Hashitoxicosis. Over the years, 16% of children presenting with overt hypothyroidism stopped therapy. Free T4 at presentation was the only predictor of outcome over time.

Conclusions:
Our findings suggest that only 26% children who were euthyroid at presentation developed hypothyroidism, whereas over 50% of those with SCH went on to require treatment. Of those presenting with overt hypothyroidism, 16% recovered with time. The only predictive parameter for LT4 therapy at the end of the study was free T4 levels at presentation. Long-term follow-up is required to determine ongoing therapy needs and screen for additional autoimmune diseases.

Fertility in Female Thyroid Cancer Patients

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Introduction:
Thyroid cancer (TC) is frequently found in young women. Concerns have been raised about the impact of TC diagnosis and radioactive iodine therapy (RAIRx) on reproductive function.

Aim:
To evaluate the effects of TC diagnosis and RAIRx on infertility (IF) and pregnancy-rates.

Methods:
The Clalit-Health-Medical-Organization computerized-database was screened to identify women diagnosed with TC at age≤40 years between 2000-2020. Rates of IF (defined as IF diagnosis and/or purchase of specific IF medications) and pregnancy after TC were compared to age-matched healthy women.

Results:
Study included 1309 women aged 30.1±6.34 years at TC diagnosis, followed for 10.8±5.7 years [680(51.9%) received RAIRx], and 5247 controls.

IF-rate in TC-patients was higher than in controls (22.9% vs. 19.8%, p=0.01), while their pregnancy-rates were comparable (44.9%/46.5%, p=0.35). Yet, in the lowest age-quartile (Time to first forthcoming pregnancy in TC-patients was longer than in controls (49.1±42.1 vs. 44.2±42.2 months, P0.001).

Among TC-patients, IF and pregnancy rates were similar in women who received/didn`t receive RAIRx, but time to first forthcoming pregnancy was longer after RAIRx(56.1±42.4 vs 40.2±40.2 months, p0.001).

Conclusions:
Our study provides reassuring evidence about the reproductive characteristics of TC-treated women. Despite a higher IF-rate and longer time to conceive (specifically in the RAI-treated women), pregnancy-rates were comparable to healthy controls. The lower pregnancy-rate in the youngest group could be attributed to psychological/social effects of cancer diagnosis at young age rather than to TC treatment.

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Thyroglobulin Point of Care Assay for Rapid Detection of Metastatic Differentiated Thyroid Carcinoma: A Pilot Study

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Introduction:
Fine needle aspiration (FNA) for thyroglobulin (Tg) measurement (FNA-Tg) and for cytology (FNAC) are recommended for the evaluation of cervical lymph nodes (LN) suspected as differentiated thyroid carcinoma (DTC) metastases.

Aim:
To assess the diagnostic accuracy of a novel point-of-care assay for Tg (POC-Tg) (Patent Application PCT/IL2022/050067), able to detect within minutes, Tg in the needle washout of a suspicious LN.

Methods:
Tg Limit of detection was set at a concentration of 5 ng/mL following needle dilution with 1 mL of 0.9% saline. The POC-Tg was assessed in the FNA clinic when a LN suspected as DTC metastasis was biopsied; and in the operating room (OR) when suspicious LN was found during thyroid surgery. Each LN was evaluated using both the formal method (FNA clinic- FNAC and FNA-Tg; OR- 'frozen-section'), and the POC-Tg. Clinical decisions were made according to the formal evaluation. The POC-Tg performance was analyzed retrospectively.

Results:
FNA clinic: 22 LN were tested. Eleven were found to be positive in both our POC-Tg and the formal Tg immunoassay, with final histology reported metastatic DTC. Ten LN were negative in both our POC-Tg and the standard Tg immunoassay, all with benign cytology. One metastatic LN was negative in our POC-Tg but showed low detectable Tg in the standard immunoassay. **OR:** Four LNs were positive and seven negative in both our POC-Tg, and the 'frozen-section' results.

Conclusion:
The diagnostic accuracy of the POC-Tg for LN metastases of DTC origin exceeded 95%, thus it might improve diagnostic and treatment algorithms.

Role of the Transcription Factor Nrf2 in the Enhancement of Paricalcitol-Induced Differentiation of AML Cells by Clinically Relevant Fumaric Acid Esters

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Acute myeloid leukemia (AML) is an aggressive hematologic malignancy, mainly in older adults, characterized by uncontrolled growth of immature myeloid blasts. Despite initial responses to standard chemotherapy, prognosis remains grim for most patients. Differentiation therapy of AML is an alternative to cytotoxic chemotherapy. Natural and synthetic vitamin D derivatives (VDDs) are powerful inducers of monocytic differentiation of AML cells in culture; however, their differentiation-inducing concentrations can be lethal in vivo due to severe hypercalcemia. We have previously shown that fumaric acid esters (FAEs), such as the clinically approved drug dimethyl fumarate and its in-vivo metabolite monomethyl fumarate (MMF), can synergistically enhance the prodifferentiation effects of near-physiologic concentrations of different VDDs [PMID: 30508646]. Since FAEs are known activators of the transcription factor Nrf2, we hypothesized that Nrf2 may mediate the enhancing effects of these agents on the differentiation of AML cells induced by 19-nor-1,25-(OH)2-vitamin D2 (paricalcitol). Here, we demonstrate that in non-transfected and empty vector-transfected HL60 human AML cells, the differentiation-inducing effect of paricalcitol was markedly potentiated by MMF, monoethyl fumarate (MEF) or the Nrf2-activating phenolic diterpene carnosic acid (CA). This potentiation was associated with a marked upregulation of the vitamin D receptor (VDR) protein levels and mRNA expression of VDR target genes, e.g. CAMP and CYP24A1. However, these enhancing effects of the Nrf2 activators were dramatically reduced in HL60 cells stably expressing a dominant-negative Nrf2 (dnNrf2) mutant that lacks the transactivation domain. Notably, co-treatment of dnNrf2-expressing cells with the glutathione precursor N-acetyl cysteine or cell-permeant glutathione ethyl ester partially restored the synergy between paricalcitol and Nrf2 activators. These data suggest that the differentiation-enhancing effects of FAEs and CA are mediated by the transcriptionally active Nrf2, possibly through the Nrf2-dependent elevation of cellular glutathione levels.

Announced Meals at will with the MiniMed™ Advanced Hybrid Closed Loop (AHCL) Reduce Diabetes-Related Distress

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Introduction:
Little is known about selective meal announcement using the MinMed™ AHCL system, designed for optimal performance with announcement of all meals.

Aims:
To compare glycemic outcomes and patient experience during MiniMed™ 780G AHCL system use while announcing all meals versus announcing meals at will.

Methods:
Participants used the MiniMed™ AHCL system at home during two 90 days phases in which they were given instructions to announce all meals (AM), and next to announce meals at will (AMW), for meals containing up to 80 grams of carbohydrates.

Results:
Fourteen subjects (10 males, mean age 44.3±11) with T1DM were enrolled, with a baseline A1C of 6.9±1%. Table 1 summarizes glycemic indices and AHCL data, demonstrating that patients chose to bolus only slightly less during AMW compared to AM (5.5 vs. 5.2 boluses), without resultant deterioration in glycemic indices (A1c 6.4 vs. 6.5%, TIR 78.1 vs. 78.8%, p=ns). Subjects surveyed regarding the option not to have to bolus for all meals experienced a significant reduction in reported effort to manage diabetes (p=0.045) and 86% endorsed worrying less about their diabetes. Most (93%) preferred the AMW phase of the study.

Conclusions:
Though the MiniMed™ AHCL system is designed for optimal performance with meal announcement, when meals containing 80 grams of carbohydrates are consumed with announcement of meals at will, there is a slight reduction in the number of daily boluses with no decline in glycemic control, yet markedly less diabetes related distress and improved treatment satisfaction.

Table 1. Glycemic Indices and AHCL Usage

	Announced Meals (AM)	Announced Meals at-Will (AMW)
Participants, n	14	14
Measured HbA1c, %	6.4	6.5
>250 mg/dL, %	3.6	3.5
180-250 mg/dL, %	15.0	14.5
70-180 mg/dL, %	78.1	78.8
55-70 mg/dL, %	2.8	2.5
<54 mg/dL, %	0.6	0.7
Daily boluses, n	5.5	5.2
Auto Mode use, %	96.9	95.3

Reduced Expression of Glucose Transporter 2 (GLUT2) in the Renal Proximal Tubular Cells (RPTCs) Attenuates Diabetic Kidney Disease (DKD)

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DKD affects more than 30% of all diabetic patients. It is strongly associated with global healthcare burden and is considered the primary cause of end-stage kidney disease (ESKD). Glucose handling in the RPTCs plays a central role in DKD pathophysiology; yet, the molecular mechanisms underlying hyperglycemia-induced tubulopathy are poorly understood. Although GLUT2 is a major glucose transporter in the RPTCs, its exclusive role and contribution to DKD are unknown. Here, we reveal its fundamental role in the pathogenesis of DKD.

By using the Cre-lox technique, we developed a novel mouse strain with reduced RPTC-GLUT2 expression, and crossed it with the Akita-diabetic mouse strain, generating diabetic RPTC-GLUT2$^{-/-}$ mice. We evaluated the renal phenotype of the RPTC-GLUT2$^{-/-}$ mice compared to their WT controls. We assessed renal patho-morphology, blood and urine biochemistry, and tubulointerstitial fibrosis and inflammation. Moreover, we measured renal glucose uptake by µPET-MRI imaging.

Whereas no significant changes were found in the weight and diabetic status of the RPTC-GLUT2$^{-/-}$ mice compared to their WT controls, considerable improvements of renal function in the diabetic RPTC-GLUT2$^{-/-}$ mice were measured, including significantly reduced urine creatinine, albuminuria, ACR, and KIM-1 levels. Interestingly, the hyperglycemia-induced pathomorphological changes in the kidney, as well as renal injury, fibrosis, and inflammation, were significantly attenuated in the diabetic RPTC-GLUT2$^{-/-}$ mice. Moreover, the renal glucose uptake was significantly decreased due to the reduced RPTC-GLUT2$^{-/-}$ expression.

Our novel observations suggest that RPTC-GLUT2 not only affects glucose reabsorption but also modulates cellular function, eventually affecting the degree of renal inflammation, tubulointerstitial fibrosis, diabetic kidney injury, and renal pathomorphology. Correspondingly, our results indicate that GLUT2-linked molecular mechanisms greatly affect DKD pathophysiology.

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The Relationship between Chrono-Nutrition, Sleep and Glycemic Control in Women with Gestational Diabetes: A Randomized Controlled Trial

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Background:
Gestational diabetes mellitus (GDM) is associated with increased risk of maternal, fetal and neonatal morbidities. Chronobiological disorders have recently been identified as risk factors for those morbidities. These include chrono-nutritional disorders - related to meal frequency and content according to the sleep-wake cycle; sleep disorders - related to sleep quality, and chrono-obesity disorders – abnormal weight gain as a result of sleep deprivation and time of eating.

Objective:
Our aim was to assess whether a chrono-nutritional and sleep hygiene intervention can improve maternal glycemic control among women with GDM.

Study Design:
This randomized controlled trial included 103 women with GDM who were carrying a singleton fetus and assigned to either an intervention group (n=33) or control group (n=70). The intervention group was assigned to a chrono-nutrition and sleep hygiene program, in addition to the usual care for GDM, from the time of diabetes diagnosis to birth. The control group received the usual GDM care.

Results:
Chrono-nutritional and sleep hygiene intervention significantly reduced the proportion of women with suboptimal glycemic control (RR=0.28, 95% CI 0.18-0.81). The impact of intervention on balancing maternal glycemic control was mainly due to the decreased carbohydrate intake in the evening interval of the day (RR=0.8, 95% CI 0.64-0.99).

Conclusion:
Chrono-nutritional and sleep hygiene intervention may improve glycemic control in women with GDM.

Keywords: chrono-nutrition, circadian, gestational diabetes mellitus, glycemic control

Central Role of mTORC1 in Mediating the Hyperglucagonemia of Diabetes

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Introduction:
Hyperglucagonemia plays an important role in diabetes pathophysiology, however the mechanisms involved are poorly understood.

Aim:
Investigate the role of the nutrient sensor mTORC1 in alpha-cell dysfunction.

Methods:
Alpha-cell mTORC1 activity was assessed in models of T1D (*Akita* mice and diphtheria-toxin-induced beta-cell ablation; DT-diabetes) and T2D (db/db mice) by immunostaining pancreatic sections and FACS-sorted alpha-cells for glucagon and pS6, an mTORC1 downstream target. We generated conditional KO of Raptor, regulator of mTORC1, in adult *Akita* alpha-cells and tested effects on glucose tolerance by IPGTT and glucagon secretion by ELISA.

Results:
Plasma glucagon and pancreatic glucagon content were 2-3-fold higher in *Akita* mice than controls. mTORC1 activity was increased in alpha-cells of *Akita*, DT-diabetes and db/db mice. Treatment of *Akita* mice with insulin or SGLT2 inhibitor dapagliflozin prevented the stimulation of mTORC1. Surprisingly, ex-vivo incubation of WT islets at high glucose decreased alpha-cell mTORC1 activity. Metabolomic profiling of plasma of *Akita* mice showed that fructose, fructose 1-phosphate and sorbitol were increased. One-week feeding WT mice with 30% fructose in drinking water increased plasma glucagon and alpha-cell mTORC1 activity. Similarly, ex-vivo incubation of islets with high fructose increased glucagon secretion and alpha-cell mTORC1 activity. Finally, plasma glucagon of alpha-cell-Raptor KO *Akita* mice was decreased and glucose tolerance improved.

Conclusion:
In diabetes, plasma fructose is increased even without excess fructose intake, leading to activation of mTORC1 in alpha-cells, thereby increasing glucagon secretion. Inhibiting alpha-cell mTORC1 prevents hyperglucagonemia and ameliorates diabetes; this may provide a novel therapeutic strategy for diabetes.

The Association Between Time in Range %, Measured by Continuous Glucose Monitoring (GCM) and Physical & Functional Indices Amongst Older People with Type 2 Diabetes

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Older people with diabetes have an increased risk for mobility disability and sarcopenia. Studies show an association between A1C and Sarcopenia. Less is known regarding the relationship with Time In Range (TIR).

Aims:
To assess among older people with diabetes type 2, the association between: TIR and aerobic capacity, gait speed, strength, balance, and frailty indices.

Methods:
A cross sectional study, in people with diabetes 60Y. Participants were provided with a blinded CGM system- (iPro™ professional CGM, Medtronic) for 1 week and underwent physical-functional assessment at two time points. The association between the % of time in range (TIR) and several physical indices was determined using linear regression.

Results:
This analysis pertains to 144 men and women.

After adjustment for age and gender, a 1% higher TIR (70-180) was associated with a 0.169 higher score on the 6-minute walk score (aerobic capacity and endurance) (P-value=0.023), 0.119 higher score on the Grip test (upper limb muscle strength (P-value=0.039)), 0.164 lower score on the 360-turn test (dynamic balance) (P-value= 0.039) and 0.165 lower score on the Timed Up & Go(TUG), (fall risk and balance) (P-value=0.037).

Conclusion:
Higher % TIR is associated with better scores on indices of muscle strength, aerobic capacity, and balance. Future studies are needed in order to elucidated if glucose levels are merely a marker of disease severity, or if there is possibly a causal relationship.

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The Relationship between Neonatal Hypoglycemia and Cord Blood C-Peptide Levels in Neonates of Mothers with Type 1 Diabetes

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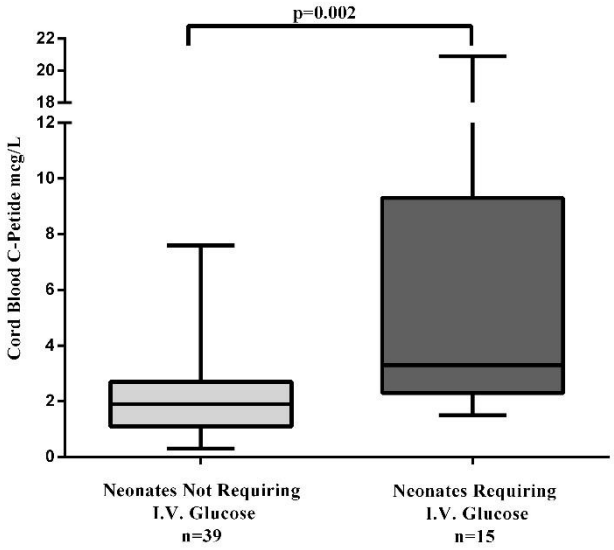
Introduction:
Neonate of patients with type I diabetes (T1D) are at increased risk for neonatal hypoglycemia. It is hypothesized that this is a result of maternal hyperglycemia and subsequent fetal hyperinsulinemia.

Aim:
The aim of this study was to determine the relationship between clinically significant neonatal hypoglycemia (CS-hypo) and cord-blood c-peptide (CBCP) concentrations in patients with T1D.

Materials and Methods:
This was a prospective cohort study including patients with T1D followed at a single tertiary center. Clinical variables and glucose control data during pregnancy were prospectively recorded. Cord-blood of neonates was collected, and CBCP concentration was determined. The correlation between CS-hypo (neonatal hypoglycemia requiring IV glucose treatment) and CBCP concentrations was determined.

Results:
This analysis pertains to 54 pregnancies. Mothers to neonates that experienced CS-hypo had longer diabetes duration than mothers to neonates who did not (19 vs. 13 years, p=0.023). No differences were observed between the groups in BMI, age, and other maternal complications, nor in glucose control indices including the levels of HbA1c (1st, 2nd and 3rd trimesters), and average glucose. CBCP was significantly higher in neonates with CS-hypo than in those who did not (3.3 mcg/L vs 1.9 mcg/L, p=0.002, Fig 1.). After adjustment for age at conception, BMI, diabetes duration, neonatal birth weight and 3rd trimester HbA1c every 1 unit higher in CBCP level was associated with a 1.46 (1.02-2.09, p=0.035) fold greater risk CS-hypo.

Conclusion:
In neonates of patients with T1D, higher CBCP levels are associated with a higher risk for neonatal hypoglycemia.


p=0.002
Cord Blood C-Petide mcg/L
22
20
18
12
10
8
6
4
2
0
Neonates Not Requiring
I.V. Glucose
n=39
Neonates Requiring
I.V. Glucose
n=15

Novel Insights into The Associations between Specific Brain Tract Segmental Alterations, Glucose Levels, and Cognitive Performance Among Adolescents with Type 1 Diabetes

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Background:
Type 1 diabetes mellitus (T1D) impacts brain function and structure, even among pediatric patients. Despite intensive management and technological interventions, most patients do not achieve glycaemic goals and have high postprandial excursions. The effects of these excursions on specific relations between cognitive performance and specific brain tract alterations in young patients are yet unknown.

Aim:
To assess the association between neurocognitive accomplishments, quantitative parameters of white matter brain architecture, and glycaemic control among adolescents with T1D and healthy siblings of similar age.

Methods:
A case-control study included 12- to 18-year-old patients with T1D (N=17, 8 males, diabetes duration of 6·53±4·1 year) and their healthy siblings(N=13). Participants underwent brain imaging, including diffusion tension imaging (DTI) and baseline neurocognitive tests. All were hospitalized for 30 hours for continuous glucose monitoring and multiple repeated neurocognitive testing as a function of controlled manipulation of food intake and pre-meal insulin administration to enable capillary glucose of 240 mg/dl versus

Results:
Mean HbA1c was 8·61±1·26, eight participants having HbA1c≤8·3. Significant associations were detected between glucose level, HbA1c, and executive function (EF), inhibition ability, and semantic and episodic memory. White matter analysis demonstrated opposite effects of diffusion coefficients in various regions according to glycaemic control, indicating specific associations between anatomical pathways and cognitive performance as a function of the group.

Conclusions:
Worse glycaemic control and transient high glucose levels are associated with lower executive function and variability in brain architecture in related areas.

Asymptomatic Familial Hyperprolactinemia Caused by a Unique Bi-allelic Variant in the Prolactin-Receptor Gene

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Introduction:
Rare cases of inherited hyperprolactinemia, related to prolactin receptor (PRLR) gene variants, present as agalactia, without hypogonadism, infertility or galactorrhea.

Aim:
To delineate the clinical phenotype and the genetic cause of familial hyperprolactinemia.

Methods:
Family members underwent clinical, laboratory and imaging assessment. Whole exome sequencing was used to obtain genetic molecular diagnosis of the proband. Segregation analysis was performed by Sanger sequencing.

Results:
We ascertained extended inbred kindred with multiple female subjects displaying presumably asymptomatic hyperprolactinemia. Seven females and 7 males, of 3 different branches and 2 generations, were evaluated. Four females of reproductive age had hyperprolactinemia (X6-10 of the upper limit of norm). All 4 had regular ovulatory cycles and no galactorrhea, and 2 conceived spontaneously. Of 3 who gave birth, only one nursed without difficulties, while 2 reported ‘lack of milk’ and did not have breast engorgement after stopping breastfeeding. Macroprolactin and prolactinoma were excluded. The four affected females harbored a homozygous PRLR(NM_000949.7):c.1750del (p.Glu584AsnfsTer49) variant, predicted to change the last 39 amino acids of the encoded protein and elongate it by additional 13 amino acids, affecting the intracellular domain of PRLR. Notably, two homozygous and 5 heterozygous males had prolactin levels within the normal range, without signs or symptoms of hyperprolactinemia.

Conclusions:
We describe a novel homozygous PRLR p.Glu584AsnfsTer49 variant predicted to affect the intracellular domain of prolactin receptor, resulting in significant asymptomatic hyperprolactinemia among females in their reproductive age, with a possible mild lactation difficulty, suggesting very mild phenotype attributed to this particular PRLR variant.

Adult Hypothalamic Otp Expression is Required for Maintaining Behavioral and Metabolic Homeostasis

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Aim:
Orthopedia (Otp) is a homeobox gene that has a crucial role in developing neuro-peptidergic hypothalamic neurons. Otp null mutant mice die soon after birth and display progressive neural impairments. Although the expression of Otp is maintained in adult hypothalamic neurons, the role of Otp in the adult is unknown. The experiments described in this work aim to study the cellular identity of Otp neurons and determine the physiological role of hypothalamic Otp in mice.

Methods:
We used immunohistochemistry and reporter mouse lines and analyzed Otp expression in specific neural subpopulations. To elucidate the role of Otp in the adult mice, we characterized a tamoxifen-induced Otp deficient mouse model lacking Otp selectively in forebrain CamKII-positive neurons (cKO). The characterization of the cKO Otp mouse model included a battery of behavioral and physiological tests.

Results:
We demonstrate that Otp is expressed by specific hypothalamic neurons that regulate energy balance and the stress response. Conditional KO of Otp alters the transcriptional response of both HPT and HPA downstream genes. We show that the altered gene expression is not due to neuronal death. We show that adult deletion of Otp leads to impaired adaptation to stressful challenges. A phenotype that was partially explained by the effects on the HPT axis function.

Conclusions:
Adult Otp emerges as a pivotal regulator in the complex interrelated networks which underlie stress response and energy balance. Hypothalamic Otp is potentially a new target in preventing and treating depression and other neuropsychiatric disorders.

Optic Pathway Glioma and Endocrine Disorders in Patients With and Without NF1

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Objective:
To assess the prevalence of endocrine dysfunction in children with optic pathway gliomas (OPGs), and to compare outcomes between those with and without neurofibromatosis type 1 (NF1).

Study Design:
A retrospective single center study using data of children diagnosed with OPGs during 1990-2020, followed at a pediatric tertiary center endocrine clinic. Growth and puberty parameters, and occurrence of endocrine dysfunction were evaluated.

Results:
The study included 59 patients (29 males); 36 (61%) with NF1. Isolated optic nerve involvement was higher among patients with than without NF1 (p0.01). Patients without NF1 were younger at OPG diagnosis (p=0.04); and more often treated with debulking surgery (p0.01) or chemotherapy (p0.01), At the last endocrine evaluation, patients without NF1 had comparable height SDS (p=0.45), higher BMI SDS (p=0.02), and a higher rate of endocrine complications (78.3% vs. 41.7%, p=0.006).

Age at the last endocrine evaluation was associated with increased incidence of endocrine disorders (OR=1.42, CI=1.10-1.83, p=0.007). Older age at diagnosis of OPG was associated with a lower risk of developing endocrine disorders (OR=0.54, CI=0.33-0.90, p=0.018). OPG location in the hypothalamus or adjacent structures was associated with a higher risk of developing an endocrine disorder (OR=11.43, CI=1.02-127.82, p=0.048).

Conclusions:
Among patients with OPG, endocrine dysfunction presented more commonly and at a younger age in those without NF1 than with NF1. This may be associated with tumor location and more aggressive treatments. The findings may dictate separate concerns in the follow-up of children with OPG with and without NF1.

Pituitary Microadenoma vs. Macroadenomas in Cushing`s Disease: Does Size Matter?

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Nirit Aviran-Barak[3],
Varda Nadler[3],
Sandra Alboim[3],
Gloria Tsvetov[1,2,3],
Dania Hirsch[1,2,3]

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Background:
Reports on the differences of clinical and biochemical behavior of adrenocorticotropic hormone (ACTH)-secreting pituitary microadenomas and macroadenomas are limited and inconsistent.

Objective:
Describe the clinical and biochemical characteristics of patients with corticotroph macroadenomas and microadenomas.

Methods:
Retrospective charts review of patients with Cushing`s disease, treated at Rabin Medical Center between 2000 and 2017, or at Maccabi Healthcare Services between 2005 and 2017. Epidemiologic, clinical and biochemical factors were compared between patients with corticotroph macroadenomas and microadenomas.

Results:
The cohort included 105 patients (82 women, 78%; mean age, 41.5±14.5 years), including 80 patients with microadenomas (mean size, 5.2±2.2 mm) and 25 patients with macroadenomas (mean size, 18.0±7.7 mm) . Baseline characteristics were similar between groups. Most common reasons for completing an investigation for Cushing`s syndrome among patients with microadenomas and macroadenomas were weight gain (46.3% vs. 52.0%, P=NS) and Cushingoid features (27.5% vs. 20.0%, P=NS). While mean urinary free cortisol levels (5.2±5.4xULN vs. 7.8±8.7xULN) and serum cortisol levels following low-dose dexamethasone (487.6±329.8 vs. 372.0±324.5 nmol/L) were higher with macroadenomas, the differences were not significant with considerable overlap between groups. Concentrations of ACTH were greater with macroadenoma (1.9±1.2xULN vs. 1.3±0.8xULN, respectively, P =0.01). Rates of recurrent/persistent disease were similar with microadenomas and macroadenomas (35.2% vs. 28.6%, respectively; P = NS), as was the rate and duration of post-operative glucocorticoid treatment.

Conclusions:
While ACTH-secreting macroadenomas exhibit higher plasma ACTH levels than microadenomas, there was no correlation between tumor size with cortisol secretion values or clinical characteristics in patients with Cushing`s disease.

The Endocannabinoid System Protects against Colon Cancer Development Via CB2

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Endocannabinoids are endogenous ligands that bind to the differentially expressed cannabinoid receptors. Cannabinoid receptor 2 (CB2) is predominantly expressed in immune and bone cells. Evidence from both *in vitro* and *in vivo* studies has established diametric roles of CB2 in inflammation and cancer. To elucidate the determinant role of the endocannabinoid system and specifically that of endogenous CB2 agonists in cancer, we used CB2 knockout ($CB2^{-/-}$) mice. We found higher incidence of spontaneous precancerous lesions in multiple organs, including the colon, in aging $CB2^{-/-}$ mice. We then investigated if the CB2 receptor attenuates tumorigenesis in colon cancer using multiple approaches. Firstly, we compared wildtype to $CB2^{-/-}$ mice receiving multi-stage chemical colorectal cancer induction using azoxymethane/dextran sodium sulfate (AOM/DSS) in female mice for 11 weeks. Secondly, we used a mouse strain with a genetic predisposition to intestinal adenomas ($Apc^{Min/+}$) and compared $Apc^{Min/+}CB2^{-/-}$ to $Apc^{Min/+}CB2^{+/+}$ mice. For mice receiving AOM/DSS, we found that the $CB2^{-/-}$ mice had higher disease activity assessed using colonoscopy, increased presence of dysplastic polyps, and a higher number of tumors. Additionally, compared to $Apc^{Min/+}CB2^{+/+}$ mice, $Apc^{Min/+}CB2^{-/-}$ mice displayed increased colonic shortening and larger and increased number of tumors in the small and large intestine: we also observed enhanced splenic population of immunosuppressive and tumor-promoting cells called granulocytic-myeloid derived suppressor cells, and a decrease in anti-tumor CD8+ T cells. Taken together, these results suggest that endogenous CB2 activation suppresses colon cancer development likely by altering the balance between pro-tumorigenic and anti-tumorigenic immune cells.

Finetuning the Immune System to be More Resilient to Stress

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Stress is a systemic physiological and behavioral response to what an organism perceives as threat. Resilience to the same stressful event varies within a population. However, it remains challenging to identify resilience in mammalian embryos to determine if stress resilience is established as a trait during development or acquired later in life.

Aim:
To understand whether vertebrates display differential stress response early in life, and to study the factors contributing to the establishment of stress resilience/susceptibility during development.

Methods:
Zebrafish exhibit stress responsive behavior early in life. We developed novel behavioural strategies to measure stress resilience in larval and adult zebrafish. To study the molecular mechanisms underlying stress resilience, we employed transcriptomic analysis.

Results:
We show that resilience is a trait in genetically identical populations that is determined at early stages of development. Stress resilience is maintained as the fish grow to become adults and is passed on to the next generation. At the molecular level, resilience is positively regulated by neuropeptides and negatively regulated by the innate immune complement pathway.

Conclusions:
Resilience is established early during development as a stable trait and is regulated by neuropeptides and the immune system.

Adipose Tissue Derived FABP4 Promotes Hepatic Glucose Production in Gestational Diabetes

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One of the most common complications of pregnancy is gestational diabetes mellitus (GDM), which may result in significant health threats of the mother, fetus and the newborn. Fatty acid-binding protein 4 (FABP4) is an adipokine that regulates glucose homeostasis by promoting glucose production and liver insulin resistance in mice models. FABP4 levels are increased in GDM and correlates with maternal indices of insulin resistance, with a rapid decline post-partum.

Aim:
To determine the tissue origin of elevated circulating FABP4 levels in GDM and to assess its potential contribution in promoting hepatic glucose production.

Methods:
FABP4 protein and gene expression was determined in biopsies from placenta, sub-cutaneous (sWAT) and visceral (vWAT) white adipose tissues from GDM and normoglycemic pregnant woman. FABP4 differential contribution in stimulating hepatic glucose production was tested in conditioned medium before and after it's immune clearance

Results:
We showed that FABP4 is expressed in placenta sWAT and vWAT of pregnant women at term, with a significant increase in its secretion from vWAT of women with GDM compared to normoglycemic women. Conditioned media from vWAT of pregnant women increased glucose production in isolated hepatocytes. Neutralizing FABP4 from vWAT secretome significantly suppressed glucose production. This effect was more pronounced in FABP4 derived from vWAT of pregnant women with GDM.

Conclusions:
This study provides new insights on the role of the adipose tissue-derived FABP4 in GDM, highlighting this adipokine, as a potential mediator of adipose tissue–liver axis in glucose homeostasis during pregnancy.

Long Term Kidney Benefits in Patients with Type 2 Diabetes (T2D) Initiating Empagliflozin vs DPP4 Inhibitors: Real World Data

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The SGLT2 inhibitor (SGLT2i) empagliflozin (EMPA) improves kidney outcomes in populations with T2D at high cardiovascular (CV) and kidney risk as demonstrated in the EMPGA-REG OUTCOME trial and in real world evidence studies. Yet, limited data is available on long term kidney outcomes with EMPA in general and lower risk populations.

In a large Israeli database (2015-2021), we compared long term kidney outcomes in patients with T2D and eGFR30 ml/min/1.73 m2 who initiated EMPA (or any SGLT2i) vs DPP4 inhibitors (DPP4i) and were naïve for both drugs 12 month prior index date. Arms were propensity score matched by baseline characteristics. Composite outcome was ≥40% sustained eGFR loss, end stage kidney disease (ESKD) or all-cause mortality. Risk was tested by Cox proportional model, adjusted to baseline eGFR.

Each arm had 7996 patients, most had no atherosclerotic CV disease history (75.5%) or were of low KDIGO risk (65.1%). Median follow up was 35.4 [IQR 20.8-52.3] months. Compared to DPP4i, EMPA arm had lower risk for the main outcome (HR 0.78; 95%CI 0.69-0.88; P0.001). Findings were consistent when any SGLT2i initiators and DPP4i were matched (HR 0.81; 0.72-0.91; P0.001), or when a composite endpoint of ≥40% eGFR loss or ESKD were analyzed.

To conclude, the long term follow up enabled to detect kidney benefits for EMPA compared with DPP4i initiation, in a general population composed mostly of patients with low cardiorenal risk.

Adipose Tissue Support of Cancer Growth is Mediated by the Adipokine FABP4

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Adipose tissue provides stromal support for tumor growth in many types of cancers by various secreted factors. Furthermore, adipose tissue dysfunction in obesity is an established risk factor not only for cardio-metabolic abnormalities, but also, as becoming increasingly evident, for increased cancer incidence and aggressiveness. Rapidly accumulating evidence suggest that the adipokine fatty acid binding protein 4 (FABP4), is an important facilitator of cancer growth and metastasis in various cancers.

Aim:
As the obesity-attributable cancer burden is likely to continue and rise, identifying FABP4 as a stromal secreted factor that promotes tumor growth represents an attractive target for pharmacological interventions in obesity-related cancers.

Methods:
We focused on two cancers that heavily depend on adipose tissue stromal support: pancreatic ductal adenocarcinoma (PDAC) that its incidence and pathogenesis are linked to obesity, and melanoma, for which the abundant adjacent sub-cutaneous adipose tissue provides key stromal support.

Results:
Both melanoma and PDAC cells proliferation and migration are markedly enhanced in-vitro by incubation with mouse adipose tissue condition medium, effects that are significantly inhibited when adipose tissue of *Fabp4* knockout (*Fabp4*$^{-/-}$) mice is used. Furthermore, the in-vivo growth of melanoma or PDAC tumors is profoundly attenuated in *Fabp4*$^{-/-}$ compared to wild-type mice. Unbiased approach to elucidate FABP4 mechanism of tumor support suggests an immune-modulatory role of suppressing antigen presentation by cancer cells, decreasing cytokine signaling and PTEN activation.

Conclusion:
Our preliminary results highlight the inhibition of FABP4 as a potential novel therapeutic approach that deprives tumors from this key stromal factor.

Bariatric Surgery Induces Gastrin Dependant Proliferation in the Stomach`s Mucosa Specifically in the EC and ECL Cells Population

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Bariatric surgery is the definitive treatment for obesity, and has positive effects on DM2 and other metabolic disorders but the mechanism is still unclear.

Gastrin is a gastric hormone that affects the secretion of HCL from the stomach and the proliferation of intestinal mucosa. In sleeve gastrectomy, most of the acid-secreting cells in the stomach are removed, leading to hypergastrinemia and possible changes in the dynamics of gastrin secretion.

In recent studies it was found that after surgery there was an increase in mucosal length (cell proliferation), both in humans and mice, the change was shown to be gastrin dependent using gastrin KO mice.

This proliferation can also be seen through the increased pan-endocrine markers in humans and mice models. And in more extensive research, using single-cell RNA-seq and histology methods it was shown that the only increased endocrine-cell populations are the EC and ECL cells.
Further analysis of the data showed an increase in CCKBR among the ECL population, a Gastrin receptor located on parietal cells and some endocrine cells. This also suggests Gastrin dependency in mediating the mucosal changes after sleeve gastrectomy.

Another marker that was increased in the ECL cell population was PTF1a, a transcription factor important for the development of the pancreas, and other organs. Indeed, factors of the exocrine pancreas are upregulated in ECL cells after surgery.

These findings, and other ongoing research at the lab, indicate that Gastrin is an important factor in the adaptation of the mucosa to the changes after sleeve gastrectomy.

A Large-scale Observational Analysis of Social Media Data Reveals Major Public Misperception of the Attainability of Drastic Weight Loss by Dieting

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Introduction:
Diet forums in social media websites provide an opportunity to glimpse the weight loss experience reported by tens of thousands of people.

Aims:
To compare weight information from individuals using different weight loss diet strategies in Reddit.

Methods:
We analyzed all postings with weight information from the six major Reddit weight-loss diet forums ("subreddits") as reported by forum participants.

Results:
Data were collected from over 55,900 users. While average start BMI is in the overweight-obese range (26-34 kg/m2), average goal BMI was in the normal range (21.5-24.5 kg/m2) in all subreddits. There is a correlation between start BMI and goal BMI (R2=0.63, p10-10) and between planned weight loss and reported weight loss (R2=0.56, p10-10). Approximately 80% of forum participants reported over 5% weight loss. Reported weight loss was less than half of goal weight loss. Average reported weight loss and adherence were highest in the Keto and loseit subreddits. More upvotes and fewer downvotes were associated with higher reported weight loss in five of the six subreddits.

Conclusions:
Despite the need for cautious data interpretation due to self-selection of users who updated weight loss and possibility of unreliable weight reports, the study has interesting findings. Goal BMIs in the normal weight demonstrate a highly unrealistic perception, in a very large lay-public cohort, of the plausibility of losing all excess weight. Success in weight loss and maintenance in self-selected individuals who continued reporting weight for many months demonstrate the subjective value some people obtain from forum participation.

A Role for Somatostatin in Regulating Weight Regain after Bariatric Surgery in Mice

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Somatostatin is a hormone and neuropeptide expressed in the pancreas, gastrointestinal tract, hypothalamus, and other tissues. It regulates directly the secretion of insulin, glucagon, many of the gastrointestinal hormones, and growth hormone. It is therefore surprising the somatostatin knockout (sst-ko) mice have a very mild phenotype. We subjected sst-ko mice and heterozygous siblings which served as controls to a high-calorie diet, and confirmed that sst-ko mice gain weight normally and have slightly more adipose tissue. Continuous glucose measurement of these mice has shown they have lower glycemia than controls. both groups of mice lost weight and regained weight at the same rate after a short transition to a normal chow diet. However, sst-ko mice did not regain weight following sleeve gastrectomy (SG), a common bariatric surgery. Sst-ko mice maintained low weight 90 days after surgery, while fed on a high-calorie diet and were leaner than heterozygous siblings that had the same procedure. SG operated sst-ko mice had low fasting insulin levels, and very rapid glucose clearance. Mechanistically, SG sst-ko mice had an exaggerated post-prandial Glp1 secretion. Post-prandial Glp1 levels were higher than in heterozygous controls that had the same surgery. Sham-operated sst-ko mice did not display an elevation in Glp1 secretion. In conclusion, by performing sleeve gastrectomy on sst-ko mice we were able to expose a role for somatostatin in regulation glycemia and weight gain, in part via regulating postprandial Glp1 secretion.

Long-Term Metabolic Effects of Non-Caloric Sweeteners

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Accumulating evidence link sugar-containing foods and beverages to adverse health outcomes. Non-Caloric Sweeteners (NCSs) are an alternative sugar source that lead to reduction in calories, and may mitigate body weight gain and hyperglycemia. Yet, contradicting studies suggest that NCSs may mediate metabolic derangements.

Aim:
To assess long-term metabolic effects of chronic consumption of NCSs.

Methods:
C57BL/6 mice consuming either regular diet or high fat diet (HFD) were supplemented with NCSs in their drinking water for ~20 weeks at concentrations consumed by humans.

Results:
Under HFD, mice consuming reb M or sucralose had significant lower body weight compared to fructose. A significant decrease in blood glucose levels was found only in mice consuming ace-k. Furthermore, all NCSs other than saccharin, resulted in significantly improved insulin sensitivity compared to fructose. Consumption of sucralose or reb M resulted in improved glucose tolerance. A trend towards higher levels of plasma insulin was observed in mice under HFD drinking either fructose or saccharin.

None of the interventions caused a decrease in fluid consumption as compared to water, nor were significant differences in daily food intake, daily caloric intake or energy expenditure. RER displayed a normal nocturnal pattern in all groups and no significant change in voluntary physical activity was observed. As compared to fructose, NCS consumption decreased markers of NAFLD in obesity.

Conclusions:
Our results indicate that chronic consumption of NCS do not result in any observed metabolic alternations, and may attenuate some of the metabolic derangements associated with fructose and high fat-based diet.

Harnessing Islet Heterogeneity to Trace the Origins of Type 1 Diabetes

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Aim:
Type 1 diabetes (T1D) is a chronic debilitating disease caused by an autoimmune attack that destroys insulin producing b-cells in pancreatic islets. Surprisingly, a century after the discovery of insulin T1D remains incurable and the factors which trigger it are largely unknown. In the early stages of the disease, different islets experience varying degrees of the immune attack, and islets infiltrated by immune cells are often adjacent to intact islets. This phenomenon presents a powerful natural experiment which provides an opportunity to find the causes for T1D by asking: “Why is islet X attacked by the immune system, while its neighbor, islet Y, is not?

Methods:
To answer this question, we developed a method to separate attacked and non-attacked islets derived from the same pancreas. This way, we avoid confounding factors which accompany the classical juxtaposition of mice from different genetic backgrounds, or mice at different stages of the disease.

Results:
Single cell RNA sequencing of attacked and non-attacked islets extracted from non-obese diabetic (NOD) mice reveals the full repertoire of immune cells in the islet niche during the pre-symptomatic phases of the disease. This facilitated reconstruction of a crude timeline of the events that lead to beta cell destruction; and revealed a potential regulatory role for a macrophage population specific to non-attacked islets.

Conclusions:
Altogether, investigating the “battlefield” which drives the diabetic process is expected to yield novel markers for early detection and points of intervention in attempt to delay, or even prevent, the eruption of the disease.

The Methylation Pattern of a Unique Bilateral Para-overian Adrenal Rest Tumor in a Girl With Nicotinamide Nucleotide Transhydrogenase Mutation

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Clinical Presentation:
A 15-year-old girl, with homozygous G200S NNT-mutation followed for adrenal insufficiency reappeared to follow-up with severe virilization and elevated serum testosterone (28.3 nmol/l) and ACTH (1500 pmol/l). Pelvic MRI and Ultrasound demonstrated one sided paraovarian round tumor. Laparoscopic exploration revealed bilateral para ovarian mesosalpinx masses involving the serosa of the Fallopian tube, (3 and 1 cm in diameter). The testosterone level normalized within one day after surgical removal of those masses (0.2 nmol/l).

Results:
Histopathology demonstrated a pattern of adrenal rest tissue with strong intracellular positive staining for adrenal markers such as SF-1, calretinin, MART1 and inhibin. The staining for ovarian characteristic markers such as PAX 8 was negative. Studying mRNA extracted from the tissue by RT-PCR revealed the positive Gene expression of Cyp17a1, Cyp21a2 and Mc2rcDNA but not Pomc. We further profiled the epigenomic profile of the tumor using the Infinium Methylation EPIC array.

Conclusion:
This study exemplifies severe virilization that resulted from a unique and rare type of ART in ovarian related tissue. The laparoscopic surgical findings indicate that imaging techniques may be insufficient in identification of such rest tumors and call for laparoscopy when clinical findings are suggestive. Using histopathology markers cDNA studies and epigenomic profiling by methylation studies, our study shows for the first time that female ART originates from adrenal cells. The growth of a functional androgen producing “tumor” indicates that functional NNT protein is NOT required for androgen synthesis in contrast to glucocorticoids and that a zona reticularis similar tissue in ART is responsive to ACTH stimulation.

Elevated Serum Free Cortisol is a Strong Predictor of Mortality in Hospitalized Patients with Covid-19 Irrespective of Dexamethasone Treatment

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Serum total cortisol has been linked to increased mortality in patients with Covid-19, but its reliability in critically ill patients is limited. We examined the association between serum free cortisol levels (SFC) and clinical outcomes in patients hospitalized with Covid-19 between 5/5/2020-1/3/2021.

Methods:
SFC was measured in blood samples collected at patient's admission, prior to medical treatment. Patients' files were reviewed retrospectively.

Results:
There were 241 patients (78% female), mean (SD) age 67.4 (18.5), of whom 47.3% received dexamethasone treatment (DT). The in-hospital mortality, 30-day mortality and the need for assisted ventilation (AV) were 8.7%, 14.9% and 18.3% respectively. SFC levels were higher in patients who died in hospital [3.74 (2.8) vs. 1.4 (0.85) µg/dl, p0.0001], or within 30 days [3.01 (2.3) vs 1.32 (0.77) µg/dl, p0.0001] or who required assisted ventilation [2.77 (2.4) vs. 1.4 (0.8) µg/dl, p0.0001]. SFC levels were significantly higher in patients with diabetes, hypertension, cardiovascular disease and chronic renal failure. The area under the ROC curve (AUC) to discriminate 30-day and in-hospital mortality was higher for SFC compared with IL-6, CRP, ferritin and LDH. SFC levels were higher in dexamethasone treated compared with untreated patients. Within treated patients, SFC levels were higher in those who died in hospital (3.58 (2.8) vs 1.56 (0.9) µg/dl, p 0.0001] or within 30 days [3.1(2.6) vs 1.56 (0.9) µg/dl, p0.0001], compared with those that survived.

Conclusions:
SFC levels strongly predict in-hospital and 30-day mortality as well as the need for AV in hospitalized patients with Covid-19, irrespective of DT.

Screening for Non-Classic Congenital Adrenal Hyperplasia Revisited: Proposal for a New Serum 17-hydroxyprogesterone Threshold for which a Cosyntropin Stimulation Test is Indicated

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Introduction:
The 250µg-cosyntropin stimulation test (CST) is used to diagnose non-classic congenital adrenal hyperplasia (NCCAH). The current recommendation to perform CST is when follicular 17-hydroxyprogesterone (17OHP) is 6nmol/L. This cut-off is derived from radioimmunoassay (RIA) data. Recently, a validated enzyme-linked immunosorbent assay (ELISA) has replaced RIA. This study aimed to determine the RIA and ELISA-based 17OHP cut-offs at which CST should be performed.

Methods:
A retrospective study at Maccabi Healthcare Services. Data were retrieved from adult females with suspected NCCAH, referred for CST during 2001–2020. NCCAH was defined as post-CST 17OHP 30 nmol/L. Serum 17OHP levels were assayed by direct RIA from 1/2000-3/2015, and by ELISA from 4/2015-12/2020. For each assay group, a ROC curve was generated and optimal pre-CST 17OHP threshold determined.

Results:
Cosyntropin testing was performed in 2409 female subjects (1564 in RIA and 845 in ELISA). The mean(±SD) age was 24.1±7years. NCCAH was diagnosed in 74(4.7%) of the RIA group and 63(7.5%) of the ELISA group. The mean(±SD) pre- and post-CST 17OHP levels were lower in the RIA group as compared to the ELISA group (4.1±6.4vs.5.9±9.0 and 9.9±15.3vs.12.3±17.3, respectively, p0.0001). The optimal pre-CST 17OHP cut-off values predicting NCCAH were 6.05 nmol/L in the RIA group (sensitivity=93.2%, specificity=91.7%) and 8.16 nmol/L in the ELISA group (sensitivity=93.7%, specificity=92.3%). When pre-CST 17OHP of 6 nmol/L was used in the ELISA group, specificity decreased to 84%.

Conclusions:
The optimal RIA-based pre-CST 17OHP cut-off was comparable with that recommended in the guidelines. The results suggest adopting a higher 17OHP cut-off when using ELISA.

High-Throughput Screen Reveals Putative Regulators of MKRN3 in the Hypothalamus

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Introduction:

Central precocious puberty (CPP) is often associated with loss-of-function mutations in Makorin Ring Finger Protein 3 (MKRN3). Moreover, hypothalamic MKRN3 mRNA levels decrease before puberty, suggesting its inhibitory role in puberty onset. Although this decrease is well established, the mechanisms that mediate MKRN3 downregulation are unclear.

Aims:

We aim to elucidate the mechanisms that regulate MKRN3 expression in the hypothalamus.

Methods:

In order to find genes whose expression correlates with that of MKRN3, we analysed publicly available RNA datasets from brain samples of rats and mice, and rat mediobasal hypothalami (MBH) through the juvenile to adulthood transition. This might indicate factors that control MKRN3 expression, as well as commonly-regulated factors and downstream targets. As a model for studying the putative MKRN3 regulators, we induced differentiation of human pluripotent stem cells to hypothalamic neural progenitor cells (NPCs).

Results:

The bioinformatic screen identified 26 differentially-expressed genes in the developing rat MBH, whose expression correlated with that of Mkrn3, many of which were differentially expressed also in the brain datasets. Some of these encode transcriptional regulators, which harbor putative binding sites on the MKRN3 promoter. The human NPCs express markers of differentiated neurons such as EMX2, FOXG1 and PAX6 as well as high levels of MKRN3, suggesting that they can be used to study MKRN3 regulation.

Conclusions:

Having identified potential hypothalamic regulators of MKRN3 through analysis of available RNA sequencing data, we are in a position to characterize their roles experimentally using a model of human hypothalamic MKRN3-expressing NPCs.

Using a Novel Animal Model to Uncover the Effects of Prepubertal Adrenal Androgens on the Reproductive Axis

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Introduction:
Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are produced by the adrenal glands at adrenarche, at least 2-3 years before the gonadal steroidogenesis at puberty. Adrenarche is considered unique to humans and some apes, but was discovered recently in Egyptian spiny mice, providing a new model to investigate the effects of adrenarche on maturation of the reproductive axis.

Main Aim:
To investigate the role of the prepubertal increase in DHEA and DHEAS during adrenarche on maturation of the reproductive axis.

Methods:
RNA sequencing was performed on hypothalami and ovaries of prepubertal female spiny mice aged 7-8 (pre-adrenarche) and 23-24-days (adrenarcheal), and pituitary mRNA analyzed by qPCR. GH3 lactotroph cells and KK-1 granulosa cells were used to validate DHEA effects on gene expression.

Results:
Hypothalamic mRNA levels of Mkrn3 decreased and Dlk1 increased in the adrenarcheal mice. Myelin-associated gene expression was lower compared to pre-adrenarche mice, however within the adrenarcheal group, expression levels were positively correlated to DHEA levels. Ovarian expression of steroidogenic enzymes and gonadotropin receptors (Fshr and Lhcgr) significantly increased in adrenarche. Pituitary prolactin and ovarian prolactin receptor mRNA levels were also elevated in adrenarche. Furthermore, DHEA treatment in GH3 cells increased prolactin mRNA levels, and in KK-1 cells increased prolactin receptor mRNA levels, suggesting a role for DHEA-induced prolactin in the ovary before puberty.

Conclusions:
Pre-pubertal adrenal synthesis of DHEA during adrenarche might regulate brain development and myelination in the hypothalamus, as well as ovarian steroidogenesis and responsiveness to pituitary hormones to promote ovarian maturation.

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Predicting Hypogonadotropic Hypogonadism Persistence in Male Macroprolactinoma

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Aim:
To study the baseline characteristics predicting hypogonadotropic hypogonadism (HH) persistence in men with macroprolactinoma following cabergoline treatment.

Design:
Retrospective cohort study.

Methods:
Male patients diagnosed with macroprolactinoma and HH that received cabergoline treatment, and reached normoprolactinemia, were included: 46 men that achieved eugonadism, and 12 men that remained hypogonadal. Patient's demographic, clinical and biochemical parameters, sellar magnetic resonance imaging (MRI) and visual fields tests were obtained.
Univariate analyses and multivariate logistic regression models for HH persistence were developed to investigate the relative contribution of the predicting factors.

Results:
Fifty-eight male patients (age, 49.2±12.6 years) with a median baseline prolactin of 1154 ng/mL (IQR, 478-2763 ng/mL) and adenoma diameter of 25.9±14.8 mm were followed for a median of 5.6 years. Twelve men (21%) suffered from HH persistence at the end of follow-up.

Baseline testosterone (1.6±0.7 vs 0.7±0.6 ng/mL; p0.01), luteinizing-hormone (1.8±1.5 vs 0.4±0.2 mIU/mL; p0.01) and follicle stimulating-hormone (3.4±2.9 vs 0.9±0.7 mIU/mL; p0.01) were lower, and prolactinoma diameter (23.7±12.8 vs 34.6±18.9 mm; p=0.02) was larger in men with HH persistence. Suprasellar tumor invasion (RR=6.6, p0.01), visual field defect (RR=3.8, p=0.01) and hypopituitarism (RR=6.3, p0.01) were associated with HH persistence.

In a multivariate logistic regression model, baseline testosterone below 1 ng/ml (OR=24.2, p=0.01), visual field defect (OR=37.6, p=0.01), and hypopituitarism (OR=22.1, p=0.02) remained independent predictors of HH persistence.

Conclusions:
In our cohort of male macroprolactinoma that reached normoprolactinemia under cabergoline treatment, 21% had HH persistence. Low baseline testosterone, visual field defect and hypopituitarism were independently associated with HH persistence.

Gender Dimorphism in Transgender Youth – Hormonal Therapy and the Balance Between Muscle, Adipose Tissue and Cardiometabolic Alterations

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Aim:
Given the importance of sex-hormones in metabolic regulation, dynamics in body composition and cardiometabolic alterations may occur in transgender persons receiving gender-affirming hormone (GAH-therapy). We sought to explore the association between muscle-to-fat ratio (MFR) and the risk for metabolic syndrome components in transgender youth.

Methods:
Body composition was assessed in 71 transgender female (birth-assigned male) and 149 transgender male (birth-assigned female) adolescents (mean age 15.9±2.5years) by bioelectrical impedance analysis (Tanita MC-780MA, GMON Professional Software) and MFR z-scores were calculated. GEE binary logistic models were applied for metabolic syndrome components.

Results:
MFR z-scores differed in a gender-specific manner; average for transgender females (*P*=0.536) and below average for transgender males (*P*0.001). Transgender females (OR=0.06,95%CI[0.02,0.23],*P*0.001) and higher MFR z-scores (OR=0.02, 95%CI[0.01, 0.06],*P*0.001) were associated with lower odds of overweight/obesity; higher testosterone levels (OR=1.08,95%CI[1.02,1.15],*P*=0.007) were associated with higher odds of overweight/obesity. Longer duration of GAH-therapy (OR=1.39,95%CI[1.03,1.86,*P*=0.029] and higher testosterone levels (OR=1.04,95%CI[1.01,1.08],*P*=0.011) were associated with higher odds of elevated BP. Higher MFR z-scores (OR=0.40,95%CI[0.21,0.76],*P*=0.005) were associated with lower odds of elevated TG. Transgender females (OR=0.01,95%CI[0.003,0.040],*P*0.001) and higher MFR z-scores (OR=0.59,95%CI[0.42,0.81],*P*=0.001) were associated with lower odds of low HDL-c. Transgender females (OR=0.39,95%CI[0.20,0.76],*P*=0.006) and higher MFR z-scores (OR=0.63,95%CI[0.45,0.87],*P*=0.005) were associated with lower odds of elevated TG:HDL-c.

Conclusions:
Our findings support the notion that GAH-therapy in transgender youth affects the balance between muscle and adipose mass and cardiometabolic alterations in a sex-specific manner. Taking into consideration socioeconomic circumstances, family history of CVD, lifestyle-related factors and psychiatric comorbidities, transgender males remained at an increased risk for cardiometabolic disease.

Bone Mineral Density (BMD) of Ultra-distal Radius: Are we Ignoring Valuable Information?

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Background:
BMD measurement of a non-dominant arm is not routinely performed during dual-X-ray-absorptiometry (DXA) test. While 1/3 radius measurement is recommended under certain circumstances, ultra-distal compartment is not used for osteoporosis diagnosis or fracture risk assessment.

Aim:
To evaluate the correlation of ultra-distal radius (UDR) BMD to prevalent fractures, fracture risk predicted by FRAX and diagnosis of osteoporosis by traditional sites.

Methods:
Women who underwent a routine DXA (including non-dominant forearm in all patients) in a tertiary medical center were included in a retrospective cross-sectional study. Risk factors relevant to FRAX calculation were assessed via a self-administered questionnaire.

Spearman correlation of UDR BMD to 10-year risks of major osteoporotic and hip fractures (assessed by FRAX) was explored. The possible added value of UDR BMD in explaining prevalent osteoporotic fractures was assessed using a multivariable regression model incorporating age and traditional osteoporosis diagnosis.

Results:
The study included 1,245 women with a median age of 66 (IQR 59-73), of whom 298 (24%) had UDR T-score ≤ -2.5 and 154 (12%) reported prior fractures. UDR BMD was significantly negatively correlated with FRAX risk score for hip and major osteoporotic fractures (R= -0.5 and R= -0.41 respectively; P0.001). UDR T-score ≤ -2.5 was associated with higher fracture prevalence (19% vs 10%; P0.001), and remained significant after adjusting for traditional BMD and age (OR 1.49, 1.01-2.19; P=0.043).

Conclusions:
UDR BMD correlates both with prior fractures and with predicted fracture risks and might pose added value over traditional DXA sites.

The Association Between Aromatase Inhibitors Initiation and Bone Health Assessment in Early Hormonal Positive Breast Cancer Patients: A Registry-based Cohort Study

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Aim:
To assess bone health evaluation and fracture prevention strategies in postmenopausal women with estrogen receptor (ER)-positive breast cancer after AIs initiation.

Methods:
An historical cohort analysis based on data from the cancer and osteoporosis Maccabi Health Services (MHS) registries from Jan 1st 2009 to Dec 31st 2019. Cases of estrogen receptor (ER)-positive breast cancer, early stages (1 to 3) were extracted. Index date was set as the first aromatase inhibitors (AI) purchase. BMI, smoking history, alcohol use, previous fractures, BMD T-scores, purchases of AI and anti-resorptive agents were collected. Kaplan-meier curves were generated to assess the time to outcomes.

Results:
A total of 7816 women were eligible, mean (SD) age at index was 64 (9.8), mean BMI 28.7 (5.4). One year after AI initiation 21% had a BMD measurement, the mean time to DXA was 2.2 (1.9) years from index. The mean lumbar spine T-score was -1.3 (1.3), mean Femoral Neck T-score -1.5 (1.3) and the mean Total Hip T-score -1.0 (1.0).

The proportion of patients treated was 38.6% and the mean time to an antiresorptive prescription was 1.58 (1.3) years. The most prevalent treatment was Alendronate (34%), followed by Risedronate (23%), Zoledronic acid (21%) and Denosumab (6%). The mean time to fracture was 6.7 (4.6) years with a cumulative incidence of 1.7% at five years.

Conclusions:
Despite the well-known excess risk for fractures of breast cancer AI treated patients, bone health assessment and preventive treatment are still partial and postponed. Strategies to increase awareness are needed.

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Safety of in Hospital Parenteral Anti Osteoporosis Therapy Following Hip Fracture: A Retrospective Cohort

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Background:
Parenteral treatment with zoledronic acid (ZA) or denosumab (DB) is considered first line treatment following hip fracture. Fever, hypocalcemia and renal injury have been described following these treatments.

Aim:
To assess rates of adverse events (AE) following in-hospital treatment with ZA and DB.

Methods:
This retrospective study included patients over age 65 admitted for rehabilitation to the geriatrics department following surgery for hip fracture, who were treated by the Soroka Fracture Liaison Service between 7/2014 and 1/2020, and received in-hospital treatment with ZA or DB. Demographic, clinical and biochemical data were collected from the electronic medical records. Albumin corrected serum calcium less than 8.5 and creatinine increase of 0.5 mg/dl or more during 30 days following treatment were considered as AE. Body temperature before and after treatment was documented.

Results:
362 patients met inclusion and exclusion criteria; 134 and 228 were treated with DB and ZA respectively. Mean change in body temperature after ZA was significant (P0.001) but below 38 and unchanged after DB, Rates of hypocalcemia were 18% and 29.1% in the ZA and DB groups respectively (p=0.009). Rates of worsening renal function were 3.9% and 4.5% in the ZA and DB groups respectively (p=0.8). In multivariable analysis pretreatment calcium was found to be associated with post treatment hypocalcemia (OR 0.294 =P=0.004). Female gender was found to be protective from renal injury (OR for 0.25 P=0.02).

Conclusion:
In hospital parenteral treatment for osteoporosis was associated with low rates of worsening renal function but not uncommonly with hypocalcemia.

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Fracture Liaison Service Increases Potent Anti-Osteoporotic Treatment Initiation and Reduces Mortality and Recurrent Hip Fractures among Patients Admitted for Rehabilitation following Hip Fracture

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Background:
Osteoporosis treatment rates following hip fractures (HF) are low. Fracture liaison services (FLS) increase rates of effective anti-osteoporosis treatment and potentially decrease mortality.

Aim:
To assess the impact of in hospital FLS on re-fracture and mortality rate.

Methods:
This retrospective study included patients over 65 years admitted to Soroka University Medical Center (SUMC) with HF, who were operated and transferred for rehabilitation at the Geriatrics department in 2 equal time periods: before and after the implementation of SUMC FLS. Data were captured from patient`s electronic medical charts including demographics, medical history, drug purchase and laboratory data before and after HF.

Results:
319 and 667 patients fulfilled study criteria for the 'pre-FLS' and 'FLS' cohorts respectively. Baseline characteristics of both cohorts were similar excluding lower eGFR and higher treatment rates of PPI and steroid in the 'FLS' cohort. Rates of endocrine consultation (93.4% vs 3.4% p001), performance of DXA-BMD scan (42.3% vs. 7.5% p0.001), and parenteral anti-osteoporosis treatment (65.2% vs 3.1% p0.001) were higher in the 'FLS' cohort. In a multivariable cox regression, adjusted for age, Charlson Comorbidity Index, and Functional Independence Measure (FIM) score, the FLS implementation decreased the composite outcome of recurrent HF and mortality in patients under, but not above the age of 80, (OR 0.55; CI 0.36-0.83, p=0.004).

Conclusions:
In hospital FLS Implementation increased rates of endocrine consultation, performance of DXA-BMD scan and parenteral treatment for osteoporosis of patients admitted for rehibilitation following HF. FLS decreased mortality and second HF rates under the age of 80.

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Epidemiology of Hip Fractures among Ethiopian-born Israelis over the Age of 50: A Preliminary Survey from the Israel National Trauma Registry (INTR) Database between 2011-2020

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Background:
Of the 160,000-member of the Ethiopian community in Israel, about 25,000 are 50 years or older, virtually all Ethiopian-born. Despite this substantial aging population (15.6% of the Ethiopian community), there is essentially no knowledge regarding osteoporosis in this unique ethnic group. This study aimed to generate preliminary data regarding the incidence of hip fractures in this agegroup of Ethiopian-born subjects, between 2011-2020.

Methods:
Data were retrieved from the INTR hip fracture registry, stratified by gender and age, and compared to those of the Israeli population of different ethnicity.

Results:
Ethiopian-born subjects≥50 yr-old comprised 0.6% of the INTR reports, while their representation in this age group in Israel was 1.24% (P0.0001). The INTR included trauma events reports on 966 Ethiopian-born subjects≥50 yr, or 3.9% of this specific age group within the Ethiopian community, while it included reports on 7.4% of people of this age group of different ethnicity (P0.0001).

Between 2011-2020, there were 194 reports of hip fractures among Ethiopian-born subjects≥50 yr (20.1% of all reports for this group). While hip fractures represented 32.3% of injuries reported for other people in this age group, P0.0001.

Among Ethiopian-born subjects who suffered a hip fracture 81/194 (41.8%) were men compared to 16175/48130 (33.6%) among people of other origin (P0.05).

Conclusions:
Older Ethiopian-born Israelis, particularly women, appear to be less prone to hip fractures than the rest of the population. Hip fracture being only a proxy for osteoporosis, a study linking fracture data with BMD is planned to further examine this question.

Does Hypoparathyroidism Protect Against Fractures?

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Introduction:
Patients with Hypoparathyroidism (HypoPT) have low bone turnover and high bone mineral density (BMD) due to the lack of PTH-mediated bone resorption. Yet, data on fracture risk is controversial.

Aims:
1. To assess fracture rate in patients with hypoPT of different etiologies. 2. To compare fracture incidence between gender and age-matched groups of post-thyroidectomy patients with/without hypoPT.

Methods:
Retrospective analysis, based on a computerized database of patients treated between 2010-2021 at a tertiary medical-center.

Results:
The study included 137 patients (91% women, age 64±13), of whom 105 (79%) had post-thyroidectomy hypoPT, and 21% had autoimmune/idiopathic etiology. Mean follow-up was 21±12 and 27 ±12 years, respectively, p=0.09. Patients with postsurgical HypoPT had significantly higher fracture risk than the non-surgical hypoPT patients (HR 9.04, 94% CI (1.31-62.19. (

Comparison of 105 patients with post-surgical hypoPT to 142 post-thyroidectomy patients without hypoPT revealed a higher BMD in HypoPT patients. Yet, the prevalence of fractures was 31% (32/105) in the hypoPT patients and 21% (30/142) in patients without hypoPTH (p=0.1) during a similar follow-up period (median 17 and 18.4 years, respectively). In both groups, the most common fracture site was the spine (50 % and 70% in HypoPT and control group, p=0.33). Most vertebral fractures were non-clinical morphometric.

Conclusion:
The relatively high BMD in patients with hypoPT is not associated with a lower fracture risk. As clinically-undiagnosed vertebral fractures are common, spinal imaging should be routinely performed, and treatment with PTH- replacement therapy should be considered in patients with increased fracture risk.

Differential Effects of Whey and Soy on Inflammation-induced Growth Attenuation in Young Rats

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The incidence of inflammatory diseases, such as IBD in children is rapidly rising. Growth attenuation commonly occurs in IBD and treatment options are limited. Growth hormone (GH) replacement therapy is not a feasible option due to GH resistance mediated by pro inflammatory cytokines. Based on our previous studies we set out to study the effect of nutrition on growth under inflammatory conditions.

Rats were treated with daily LPS injections, until an effect on the EGP was achieved. Subsequently animals were fed normal chow (NC) or diets containing whey or soy as the sole protein source either during LPS injections or after their termination (recovery model). Body and spleen weight, food consumption, humerus length and EGP height were measured.

Food consumption was similar between the groups, in all models. However, body weight in the LPS treated rats was 10% lower compared to untreated controls. Whey and Soy diets led to further reduction in weight. The weight of the spleen was significantly greater in LPS group indicating present inflammation. Unexpectedly, whey fed rats had normal weight spleens. LPS led to decrease of 11% in EGP height on NC, and this reduction was also corrected by whey but not by soy. Similarly, in the recovery model, whey fed animals showed a significantly higher EGP compared to soy fed group.

We have shown that LPS induced inflammation attenuates growth, by decreasing the EGP height and that whey based diet can correct this effect. Moreover, we show here that nutritional therapy, may mitigate inflammation.

E-Poster Presentations Abstracts

Revealing the Anti-cancer Region within KL1 Subunit of the Hormone Klotho

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Background:
Klotho is a 1012 amino acids transmembrane protein, composed of two internal repeats, KL1 and KL2, that can be cleaved, shed and act as a circulating hormone. Klotho regulates several pathways, including fibroblast growth factor 23 (FGF23) and the Wnt-β/catenin. Our group and other labs identified klotho as a potent tumor suppressor in various cancer types, and identified KL1 as the domain responsible for this activity. Yet, the mechanism mediating anti-cancer activity remains unresolved.

Aim:
Reveal the region within KL1 that mediate the anti-cancer activity and reveal the mechanism of action.

Methods:
We used MCF-7, MDA-MB-231, PANC1, MIAPaca-2, HCT116 and HT29 cancer cell lines. Cells were transfected with a series of C and N -terminal KL1 truncated expression vectors. Wnt-β/catenin pathway was studied by monitoring it transcriptional activity and expression of Wnt3A. Tumorigenic activity was studied by colony formation assay.

Results:
Over expression of C-terminal truncated vectors showed that KL340 is the shortest plasmid that retained ability to inhibit colony formation. None of the N-terminal truncated vectors was able to inhibit colony formation. In accordance with these results, only KL1 and KL340 decreased the levels of wnt3a and inhibited Wnt-β/catenin transcriptional activity.

Conclusion:
This study reveals that klotho's anti-cancer resides within the 340 amino acids N-terminal region. The correlation between the anti-cancer activity and Wnt-β/catenin pathway suggest this pathway plays a role in mediating anti-cancer activity. It is still yet to be determined the precise mechanism KL340 affects this pathway.

Outcomes of Patients Treated According to a New Protocol for the Management of Diabetic Ketoacidosis in the Hillel Yaffe Medical Center

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Introduction:

DKA is a frequent and life-threatening complication of diabetes. The burden of hospitalized patients with DKA and the varied protocols, together with new findings revealed in recent literature, necessitated the formulation of a uniform protocol for the management of DKA. The new protocol was based on five principles: (1) definition of DKA severity; (2) POC measurement of beta-hydroxybutyrate; (3) administration of a subcutaneous long-acting insulin within two hours after DKA diagnosis; (4) use of SC insulin for mild cases; (5) use of fixed-dose IV insulin infusion for moderate and severe cases. Implementation of the protocol and patients` outcomes were studied.

Methods:

This is a prospective study, with retrospective control conducted in 2019-2021.

Outcomes:

The 48 patients included in this study (age: 43±19 years, women 26/48) were divided into two groups, Group 1- before and Group 2- after implementation. Baseline characteristics were similar except the precipitating factors: Low compliance in Group-1, vs. SGLT-2 inhibitor treatment and more new cases of diabetes in group-2. Time from admission to first long-acting insulin administration was shorter in Group 2; median 11hours (range, 2-32.3) vs. 24hours (range, 13.9-35.6) (p=0.034), and more patients with severe DKA were admitted to the ICU 81.8% vs. 33.3% (p=0.036). There was a trend towards shorter time to DKA resolution, fewer hypoglycemic, hyperglycemic, and rebound DKA episodes, although it did not reach statistical significance.

Conclusion:

The new protocol brought uniformity in definition and management of DKA. Further research should take place in order to examine patients` outcomes, medical staff satisfaction and system resource management.

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מלון ענבל, ירושלים

Cushing Syndrome in Older Women: Age-Related Differences in Disease Origin and Clinical Manifestations

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Objective:

Determine age-related clinical presentation, biochemical profile, and cause of non-malignant Cushing syndrome (CS) in women.

Methods:

Retrospective charts review of women with pituitary or adrenal CS, treated at Rabin Medical Center between 2000 and 2017, or at Maccabi Healthcare Services in Israel between 2005 and 2017. Patients were classified into 3 groups, according to age at diagnosis: ≤45 (young), 46-64 (middle-age), or ≥65 (elderly) years.

Results:

The cohort included 142 women (mean age, 46.0 ± 15.1 years), including 81 (57.0%) with adrenocorticotropic hormone-producing pituitary adenoma, and 61 patients (43.0%) with adrenal CS: 68 young, 55 middle-aged, and 19 elderly women.

Pituitary CS was more common among young patients (48 patients, 70.6%), compared with middle-aged (27 patients, 49.1%) or elderly women (6 patients, 31.6%) (P 0.05).
Among patients with adrenal CS, hypercortisolism was diagnosed following an adrenal incidentaloma detection in 15.0% of young and 53.8% of elderly women (P 0.001).
Mean urinary free cortisol levels were highest for young women (5.03±3.6xULN), followed by middle-aged (4.80±6.0xULN) and elderly (3.5±2.6xULN) women (P 0.001), without serum cortisol differences following low-dose dexamethasone.

Weight gain was evident in 57.4% of young women (60.0% pituitary, 56.3% adrenal), compared with 15.8% of elderly women (50% pituitary, 0% adrenal) (P = 0.011).

Conclusion:

Older patients with CS have distinct disease cause and presentation, as pituitary source is less common than adrenal CS, the latter is associated with milder hypercortisoluria and is frequently diagnosed incidentally. Weight gain was prevalent in young women, and uncommon in older women.

New-Onset Diabetes Mellitus or Diabetic Mellitus Exacerbation and Pancreatic Cancer

Nirit Aviran Barak

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The relationship between new-onset Diabetes Mellitus, or rapid exacerbation of underlying Diabetes Mellitus without a known trigger, and pancreatic cancer is complicated.

Accumulating evidence shows that in stable well-controlled Diabetic patients, with rapid deterioration of Diabetes control that cannot be explained by a change in diet, weight or compliance, one should consider pancreatic imaging to exclude Pancreatic Cancer.

This also applies to patients presenting with new-onset Diabetes Mellitus.

However, there is still no consensus or definitive guidelines regarding this issue.

I aim to investigate this issue and examine the need for new guidelines regarding this topic.

In this case, I describe a 55-year-old female patient with Morbid Obesity, an underlying Psychiatric condition, and Type 2 Diabetes Mellitus, which had previously been well controlled, who presented at our clinic with a rapid deterioration of her Diabetes control.

We assumed that the deterioration of her Diabetes control was related to her diet and her underlying psychiatric disease.

Three months later she presented with Sepsis and during the inpatient investigation, she was diagnosed with Metastatic Pancreatic Cancer and from which she died a week later.

Conclusions:
My conclusion is that there is a need to consider adding additional imaging guidelines regarding the new onset of Diabetes Mellitus or an unexplained deterioration of underlying Diabetes Mellitus, about a possible underlying diagnosis of Pancreatic Cancer. There are a few questions that need to be addressed regarding this topic: When to suspect and when to perform abdominal imaging, Is it helpful or useful to do abdominal imaging or is it redundant because it will not change the disease progression

Mercaptizol induced Hypoglycemia: A Case Report

Nirit Aviran Barak

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A 22-year-old female Ashkenazy Jewish previously healthy complaint on weakness

In glucometer, her sugar level was 50 mg% and she felt better after ingestion of a small amount of sugar.

3 weeks ago while traveling in Peru, she developed thyrotoxicosis and was started mercaptizol 30 mg a day and deralin.

She didn't drink iodine (iodinated preparations for water purification) while traveling and had no pain or fever. In physical examination there where no goiter or exophthalmos
While I saw her she was already euthyroid and felt quite good except for tiredness.
In literature, we found few case reports of mercaptizol and PTU-induced insulin autoantibodies which cause symptomatic hypoglycaemia.
Most cases were described in the Asian population and resolved a few weeks after stopping the drug.
In our patient, the hypoglycaemia resolved after only one episode.
We don't have the insulin level nor antibodies titer yet.
My conclusion is that physicians should be aware of Mercaptizol and PTU induced hypoglycemia which can be life-threatening

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Non-Functioning Pituitary Macroadenomas – Long-Term Surveillance without Intervention

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Introduction:
The treatment strategy for non-functioning pituitary adenomas (NFPA) includes surgery, radiotherapy, medical treatment, or follow-up. Series of non-operated patients with NFPAs who were followed-up without intervention are limited and included only a small number of patients. This study investigated the natural history of patients with NFPAs who were followed-up without intervention.

Methods:
This retrospective study performed at Rabin Medical Center, included patients with NFPA10 mm who were naïve to surgery or medical treatment, and followed 12 months after diagnosis. Follow-up included evaluation of tumor size by MRI, visual disturbances, and hormonal levels. Follow-up terminated if the patient underwent surgery, received Cabergoline or was lost to follow-up. Tumor growth was defined as maximal diameter increase of 2mm or more.

Results:
The cohort included 50 patients (30 males) with a mean age at diagnosis of 69.0±12.0 years. The average maximal tumor size was 17.6±6.0 mm. Mean follow-up was 5.8±5.1 years. Increase in tumor size occurred in 17 patients, with an average growth of 5.1±4.2 mm. Reduction in tumor size occurred in 13 patients, with a mean decrease of 4.3±2.8 mm. Overall, 33 patients (66%) were observed without intervention and 17 patients were operated (n=3) or treated with Cabergoline (n=14) because of tumor growth, symptoms appearance or proximity to the optic chiasm. Age, gender, tumor size, invasiveness, visual disturbances, and hypopituitarism were not predictors of adenoma enlargement.

Conclusion:
Observation alone without intervention for macroadenomas should be considered in selected patients. This study did not identified predictors of tumor growth.

A Technology Based Model for Physical Capacity (gait- speed, balance and aerobic) Measurement in Older People with Diabetes

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Diabetes is a risk factor for physical disability reduced physical capacity and sarcopenia.

The aim of this research was to develop a novel parameter indicative of the physical capacity of the older person with diabetes. This parameter would allow tailoring of a personalized treatment strategy aimed at preservation of physical capacity, maintenance of functional state and improvement of quality of life.

Using the built-in accelerometer & gyro of a regular mobile phone, an individual's ongoing movement data was collected to a SW platform. Subjects were asked to attend 2 sessions one week apart. In the 1st visit they were provided with the application on their cell phone & an ActiGraph accelerometer device for the whole week. In the 1st & 2nd visit a comprehensive assessment conducted by a physiotherapist including gait speed, balance & aerobic capacity was conducted.

This analysis pertains to the first 31 older people with diabetes that were recruited. 42 independent features were created from the accelerometer readings (XYZ). Correlation analysis to find statistically significant features associated with the scores on the physical assessment tools was conducted using stepwise multi linear regression model to estimate the proportion of the variance in participants' physical capacity indices explained by the accelerometer readings (R2). The following table depicts these preliminary results:

Physical capacity	Upper body strength	Lower body strength	Dynamic balance	Risk for falls	Gait speed	Aerobic capacity	Static balance
R^2	65%*	53%*	39%	13%	99%*	13%	59%*

*$p<0.05$

The larger planned cohort will allow further validation of these results.

Different Effects of Soy and Whey on Linear Bone Growth and Growth Pattern in Young Male Sprague-dawley Rats

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Aim:
The most effective environmental factor that affect longitudinal growth is nutrition. The aim of this study was to check if the identity of specific dietary proteins affects the efficiency of linear growth.

Methods:
Different Effects of Soy and Whey on Linear Bone Growth and Growth Pattern in Young Male Sprague-Dawley Rats Young male Sprague Dawley rats fed ad libitum with either Whey (animal source) or Soy (vegetarian) based diets, matched for calories, macro- and micro-nutrients were followed for 11, 24 or 74 days. At sacrifice, humeri length and growth plate (GP) height and organization were measured.

Results:
In short-term experiments, the soy fed group consumed more food, and were heavier with longer humeri, greater Diafhyseal Diameter and better moment of inertia mesuraments while the EGP height was greater in the whey group. Interestingly, the effect on weight and humeri length after 74 days was diminished; however, the EGP height of the whey fed group was still greater, better organized and showed better bone composition as higher cortical thickness and greater mineral density

Conclusions:
The higher and better organized EGP in the whey group suggests a better growth potential with whey-based diets compared to the soy based diet, although in both cases the protein contains all amino acids required.

Studying the interaction between skeletal growth and nutritional factors may lead to the establishment of better nutritional and therapeutic regimens for more effective linear growth in children with malnutrition and growth abnormalities.

Expanding the Phenotype of Familial Hypocalciuric Hypercalcemia Type 3

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Introduction:
Familial hypocalciuric hypercalcemia (FHH) is a rare mostly asymptomatic genetic disorder affecting the calcium sensing receptor (CaSR) and its associated proteins with autosomal dominant inheritance. Mutation in AP2S1 gene is responsible for FHH3.

Aim:
Expand the phenotype of FHH type 3.

Methods:
Clinical and biochemical characterization of a patient with de-novo FHH3 mutation.

Results:
S.Z, A 30-year-old man was hospitalized for recurrent pancreatitis. His medical history included chronic hypercalcemia in the range of 11.7-13.3 mg/dl attributed to his prior clinical diagnosis of FHH. Abdominal imaging and lipid profile were unremarkable. The working diagnosis was of hypercalcemia-related acute pancreatitis. He was treated conservatively with resolution of symptoms and normalization of serum amylase and lipase. A multi-gene panel that was performed (INVITAE) revealed a heterozygous mutation in the AP2S1 gene- p.Arg15Leu. His parents and two siblings were normocalcemic. A second genetic panel for pancreatitis related genes was negative.

DXA bone mineral density revealed Z score of -2.3 at LS and -2.9 at FN and TH - a typical finding in FHH3 patients. Cinacalcet at a dose of 120mg daily was well tolerated and normalized calcium levels with no episodes of pancreatitis within 26 months of follow-up. His three-year-old son is followed for speech delay and was found to be hypercalcemic; he carries the same AP2S1 mutation.

Conclusions:
We describe a family with a de novo mutation in the AP2S1 gene presenting with recurrent pancreatitis, low bone mass and speech delay thus expanding the phenotype of FHH3.

Hybrid Insulin Management using Pump Combined with Long-acting Insulin in Youth with Type 1 Diabetes - May Be a Lifesaver: National Real-life Experience

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Background:
The utilization of CSII in type 1 diabetes (T1D) is associated with increased risk of diabetic ketoacidosis (DKA). The rationale behind using hybrid modality: long-acting insulin and CSII, is the prevention of insulin delivery failure and subsequent hyperglycemia and DKA.

Aims:
To explore the hybrid treatment modality in clinical practice in youth with T1D.

Methods:
Multicenter, observational study of youth with T1D. Data was extracted from the medical records at initiation of the hybris therapy, after 6 months, and at last visit.

Results:
Fifty-five patients (52.7% males) were treated with hybrid therapy, median age at initiation 14.5 [IQR 12.4, 17.3] years, HbA1c 9.2 [IQR 8.2, 10.2], mean glucose levels 221 mg/dL [IQR 181, 226] and treatment duration 18 [IQR 12, 47] months. Hybrid treatment was initiated due to fear of sustained hyperglycemia in 41.8%, DKA episodes in 30.8%, refusal to use CSII continuously in 14.6%. HbA1c did not change significantly throughout follow-up (P=0.262). Mean glucose levels decreased after 6 months (P= 0.034), and remained stable thereafter (P=0.274,p=0.641). Mean Ffrequency of DKA per month per patient decreased after 6 months from 0.073 (min 0,max 0.5) to 0.020 (min0, max 0.5), p=0.011, and at end of follow up to 0.016 min 0,max 0.25), p=0.007. (4 events/4 patients), and at end of follow up (10/10), compared with baseline (24/14) (P=0.002, P=0.031).

Conclusions:
Our findings suggest that this hybrid therapy is a feasible option in the management of youth with T1D, which may reduce the risk of DKA episodes.

Pituitary-Adrenal Axis Insufficiency among Hemodialysis Patients

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Background:
The diagnosis of hypocortisolism is challenging in hemodialysis (HD) patients due to shared clinical features between renal failure and cortisol deficiency.We hypothesize that in some of HD patients we miss cortisol deficiency.

Methods:
A prospective cohort of 56 HD patients(mean age 65.3±13.1, females 80%) was studied. Low dose (1 mcg) adrenocorticotropic hormone (ACTH) test was performed on all patients and blood tests for cortisol, ACTH, insulin like growth factor 1 (IGF-1),triiodothyronine (TSH),free thyroxine (FT4),renin and aldosterone, were obtained before hemodialysis session. Adrenal insufficiency was defined as a peak serum cortisol level of

Results:
25% Out of the study population had an abnormal ACTH test. Mean systolic blood pressure in the group with abnormal ACTH test was 135.2±22.0 mmHg with no difference in blood pressure in multivariable models between the groups of HD patients with abnormal and normal ACTH test. Neither differences were observed in electrolyte levels, nor in renin/aldosterone levels between these groups. Baseline ACTH level predicted an abnormal ACTH test in the study population in both, univariate and multivariate analyses. For each pg/ml increase in baseline ACTH concentration the odds for abnormal ACTH test was 1.15 (95% CI:1.03 to 1.29). In addition, IGF-SDS (standard deviation score) higher than -0.04 significantly decreased odds for hypocortisolism (OR 0.14, 95% CI: 0.02 to 0.81)in multivariable logistic regression models.

Conclusions:
We offer routine testing of hypophyseal-adrenal axis function to detect adrenal insufficiency in HD patients even in the absence of markers characteristic of hypocortisolism.

Generation and Characterization of a Mouse Model for one Anastomosis Gastric Bypass Surgery

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Objective:
One Anastomosis Gastric Bypass (OAGB) surgery became a common bariatric procedure in recent years. In this surgery, the distal stomach, duodenum, and proximal jejunum are bypassed, leading to weight loss, improvement in metabolic parameters, and a change in hormonal secretion. We sought to generate and characterize a mouse model for OAGB.

Methods:
Mice fed for 26 weeks on a high-fat diet were assigned to OAGB, sham surgery, or caloric restriction and were followed for fifty more days on a high-fat diet. Physiological and histological parameters of the mice were compared during and at the end of the experiment.

Results:
OAGB-operated mice lost weight and displayed low levels of plasma lipids, high insulin sensitivity and rapid glucose metabolism compared with sham-operated mice. OAGB-operated mice had higher energy expenditure, higher levels of Glp1 and lower albumin than weight-matched calorie-restricted mice. There was no difference in the histology of the endocrine pancreas. The livers of OAGB mice had little hepatic steatosis, yet presented with a large number of phagocytic cells.

Conclusions:
The OAGB mouse model recapitulates many of the phenotypes described in patients that underwent OAGB, and enables molecular and physiological studies on the outcome of this surgery.

A Simple Method for Continuous Glucose Measurement in Mice

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The ability to measure glucose levels in freely behaving mice is important for basic research. Here we present a simple method to implant a commercially available FreeStyle Libre continuous glucose monitor (CGM) device on the backs of the mice at a relatively low cost - the cost of the device itself. The CGM device is attached to the mice in a short (15minutes) surgical procedure in which the sensor is manually inserted under the skin of the mouse, and the rest of the CGM is sutured rather than glued to the skin of the mouse. The device functions for several days, up to two weeks, in which the mice move and feed freely. Mouse handling after the surgery is minimal, as data collection does not require any handling of the mouse and is done from outside the cage by a commercial receiver. Data analysis is demonstrated by comparing glycemia of wild-type and somatostatin knockout mice fed with a high-fat high-sucrose diet. The methodology can be easily adapted to other CGM devices.

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Validation of a Multi-Frequency Bioelectrical Impedance Analysis Device for the Assessment of Body Composition in Older Adults with Type 2 Diabetes

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Aim:
In this study, we examine the accuracy of a direct segmental multi-frequency bioelectrical impedance analysis (DSMF-BIA) (InBody 770) for assessing body composition in older adults with T2DM when compared to DXA.

Methods:
84 older adults (49 women, age 71 ± 5 years. Body mass index 30 ± 5.6 kg /m2) with T2DM who were recruited for the CEV-65 study and had both DSMF-BIA and DXA assessments at baseline were included in the analysis. The main analysis included Bland-Altman plots and Intra Class Correlation Coefficients (ICC). Sub-analyses were performed according to gender and following 10 weeks of intervention (diet, circuit resistance training, and Empagliflozin).

Results:
The leg lean mass results according to DSMF-BIA and DXA were 14.76 ± 3.62 kg and 15.19 ± 3.52 kg respectively, however, did not differ between devices according to Bland-Altman analyses (p=0.353). Assessment of appendicular skeletal mass index did not differ between DSMF-BIA and DXA (7.43 vs. 7.47 kg/m2; p=0.84; ICC=0.965, p0.0001; bias of -0.068, p =0.595). The accuracy of DSMF-BIA was limited when estimating fat mass indices reflected by significant biases according to Bland-Altman analyses.

Summary:
In a sample of older adults with T2DM the degree of agreement between DSMF-BIA and DXA, was high, supporting the use of DSMF-BIA for the diagnosis of low muscle mass. Better accuracy was observed when comparing parameters of lean mass versus parameters of fat mass. Gender as well as three common treatment modalities for T2DM did not modify the accuracy of the DSMF-BIA when compared to DXA.

Congenital Hypothyroidism can Dictate the Mode of Delivery and Intra-labor Medication Usage

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Aim:
Pregnancy and parturition reflect the complex interaction between physiologic conditions of the mother and her offspring, and fetal health characteristics may affect maternal health throughout pregnancy and delivery. We aimed to investigate the characteristics of the mother-infant dyad of term infants detected as having congenital hypothyroidism (CH).

Methods:
A retrospective cohort study of 108,717 term infants delivered liveborn at Lis Maternity and Women`s Hospital between 2010 and 2017. Infants were detected by the National Newborn Screening Program as having congenital hypothyroidism (131, 0.12%). Three years of surveillance in the Pediatric Endocrine Clinic revealed that 65 had transient CH and 66 had permanent CH. Data on maternal, pregnancy, delivery, and perinatal characteristics of the mother-infant dyads were retrieved from the hospital's electronic database.

Results:
Mode of delivery differed: a higher proportion of deliveries of CH infants required vacuum assistance, and more infants with CH were born through a cesarean section compared to the general population (p0.001). Medication during labor also differed, with higher rates of oxytocin (p0.001) and antibiotics (p=0.008) administered to mothers of CH infants. A multivariate logistic regression model revealed an increased demand for oxytocin administration during the labor of a CH infant in a hypothyroidism severity-dependent manner, expressed as a threefold risk associated with permanent but not transient CH.

Conclusions:
Our findings of increased utilization of medical interventions during the labor and delivery of CH infants suggest that the prenatal fetal thyroid function may affect the development and progress of labor and delivery, in response to oxytocin.

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Muscle-to-Fat Ratio for Predicting Metabolic Syndrome Components in Children with Overweight and Obesity

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Aim:
Pediatric obesity has been linked to the components of metabolic syndrome (MetS: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure and insulin resistance). Data on the role of muscle mass in the development of MetS are sparse. We explored the interaction between the muscle-to-fat ratio (MFR) and MetS components in children with overweight or obesity.

Methods:
An observational study of 210 pediatric subjects (88 boys, mean age [±standard deviation, SD] 11.9±3.1 years, body mass index z-score range 1.036-3.140) from January 2018 to January 2021. Body composition was measured by bioelectrical impedance analysis (BIA, Tanita MC-780 MA and GMON Professional Software), and MFR z-scores were calculated.

Results:
The 148 subjects (70%) who had MetS components were older (P=0.008), had lower socioeconomic positions, higher triglyceride/high density lipoprotein-cholesterol ratios, fat percentages (FATP), truncal FATPs (TRFATPs), and lower MFR z-scores (P

Conclusions:
Given the strong predictive value of the MFR z-score in the development of early-onset metabolic syndrome components, preventive strategies should apply interventions for improving the body composition parameters of both adiposity and muscle.

Exploring the Epigenetic Fingerprint of Sedentary Behavior

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Aim:
Exercise was reported as a stimulator of epigenetic modifications of the chromatin in muscle nuclei (myonuclei); however, it is unclear whether muscle inactivation affects the epigenetic landscape of somatic musculature. We developed an experimental animal-model imitating sedentary behavior in which chromatin epigenetic landscape could be explored.

Methods:
Third-instar *Drosophila* larvae carrying a temperature-sensitive mutation in *shibire* gene, coding for GTPase involved in neuronal synaptic vesicle transport, were used. *Shibire* homozygous mutant larvae are paralyzed at restrictive temperature (~29°C) due to inhibition of neuromuscular junction vesicular transport; muscle contraction is abolished without affecting other systems. *Shibire* and control (*y,w*) larvae were held at 18°C, or 30°C without food for six hours. Larvae were dissected, fixed and double-labeled with antibodies specific for active and repressive epigenetic marks H3K9ac and H3K27me3, respectively.

Results:
At the restrictive temperature (30°C), *shibire* mutant larvae were paralyzed in contrast to control (*shibire* at 18°C). In myonuclei of sedentary *shibire* larvae the repressive mark H3K27me3 decreased significantly relative to similar larvae grown in non-restrictive temperature (p0.001), and the active/repressed ratio of epigenetic marks (H3K9ac/H3K27me) increased (p0.001). Epigenetic activation (H3K9ac) did not differ between sedentary and mobile *shibire* larvae. In contrast, in the control (*y,w*) the active/repressed (H3K9ac/ H3K27me) ratio decreased (p0.001).

Conclusion:
In this study, modelling sedentary behavior in youth, muscle inactivity changed the epigenetic fingerprint in myonuclei, with a balance shift towards decreased chromatin methylation relative to acetylation, suggesting decline in the epigenetic control of gene transcription, and reminiscent of decreased epigenetic repression described with aging.

Breastfeeding Improves Postpartum Oral Glucose Tolerance Test in Gestational Diabetes Population, Prospective Case-Control Trial

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Introduction:
Breastfeeding is the normative form of nutrition for newborns, according to both the World Health Organization (WHO) and other international medical societies. Breastfeeding is a hormonal-dependent process, therefore maternal endocrinopathies, including maternal diabetes, may hinder the process. During pregnancy, maternal diabetes is categorized into diet-controlled only (GDMA1) or medication-controlled (GDMA2). Both categories of GDM are at an increased risk for future DM-II after delivery, however the data regarding the potential effects of breastfeeding on future diabetes mellitus (DM) type II, is scarce.

Aim:
Evaluation of breastfeeding impact amongst GDM mothers, on the rate of type-II DM diagnosed postpartum.

Methods:
This is an ongoing prospective randomized controlled trial, of pregnant individuals with GDM.

After delivery, participants were contacted by telephone and were inquired about breastfeeding and other feeding options and 75g oral glucose tolerance test (OGTT) results.

Results:
After delivery, 45 participants reported breastfeeding (BF) vs. 27 who did not BF at all. Demographic data were similar for age, gravidity and parity, and newborn's delivery weight. At 75gr OGTT, BF group had a lower fasting glucose level (91.8 mg/dL vs 103.9 mg/dL, p-value =0.002), and 2hr glucose level (96.8 mg/dL vs 108.0 mg/dL p-value= 0.1). There were more participants with impaired fasting glucose (IFG) at the BF group (5 vs. 2), whereas 2 had DM-II at the non-BF group (and none at the BF group)

Conclusions:
Amongst GDM patients, breastfeeding is associated with lower fasting glucose levels and a lower 2hr OGTT. Further research is needed to assess breastfeeding`s effect on DM-II.

The Protective Effect of Carotenoids, Polyphenols and Sex Hormones on Skin Cells under Oxidative Stress

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Skin ageing is influenced by several factors including environmental exposure, hormonal changes and oxidative stress. Reactive oxygen species (ROS) can be formed by extrinsic factors, such as sun exposure, or can result from mitochondrial dysfunction, which occurs during ageing. ROS activate the nuclear factor-kappa B (NFκB) transcription systems leading to inflammatory processes and increased production of matrix metalloproteinase (MMPs) by skin cells, which leads to collagen degradation. Several studies have shown the protective role of estrogens and of various phytonutrients on skin health.

Aim:
To examine the damage caused by ROS that originate in the mitochondria due to its dysfunction, or by H2O2, and to examine the protective role of phytonutrients, estradiol, and dihydrotestosterone.

Methods:
Human dermal fibroblasts and keratinocyte were used to determine ROS levels, measured by FACS, and their effect on cell viability by XTT assay, ELISA determined MMP1 and pro-collagen secretion as markers of skin damage. Rotenone was used to cause mitochondrial dysfunction.

Results:
Rotenone leads to ROS production, cell death, upregulation of MMP1 secretion and decreased collagen secretion. This was accompanied by activation of the antioxidant response element/Nrf2 (ARE/Nrf2) and NFκB transcriptional activity. Pretreatment with dietary compounds and hormones reduced ROS level, cell viability, and MMP1 secretion and increased pro-collagen secretion.

Conclusion:
These effects can be partially explained by the increased activity of the ARE/Nrf2, and the decreased activity of NFκB transcriptional activities. This study indicates that phytonutrients and sex hormones protect skin cells from ROS-induced damage and may improve skin health and appearance.

131I-Iodo-cholesterol Scintigraphy for Primary Aldosteronism Lateralization in a Patient with Polycystic Kidney Disease

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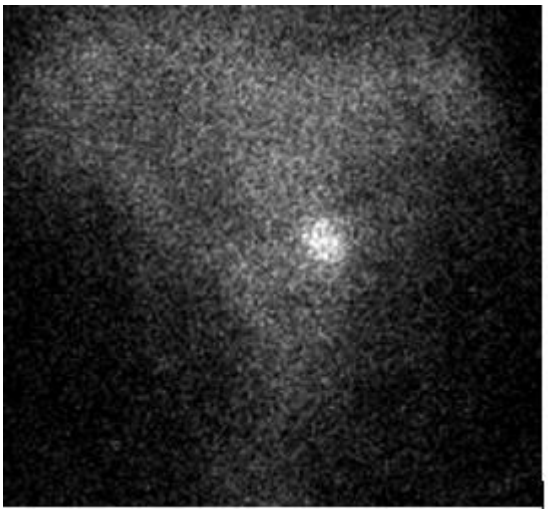
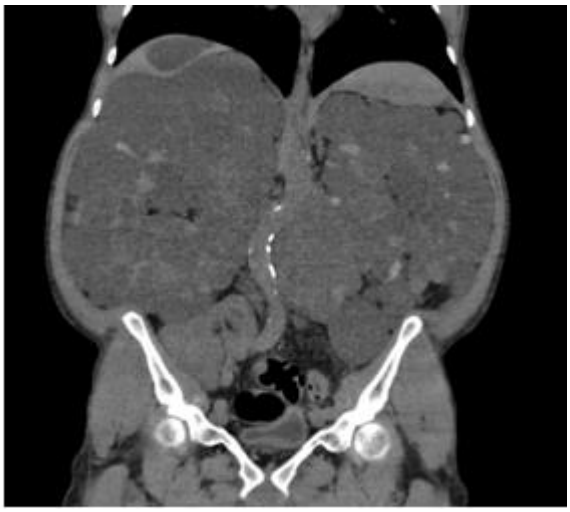
A 65-year-old male presented to our endocrinology clinic for further evaluation and treatment of primary aldosteronism (PA). Past medical history was notable for a kidney transplantation 17-years earlier due to polycystic kidney disease (PKD), and a diagnosis of PA, first established at age 52. As the patient had initially refused surgical management, no attempt at PA sub-type classification was pursued and he was medically managed with spironolactone. Over the years, blood-pressure control was poor and the patient became hypokalemic, despite large amounts of potassium supplements.

Due to the mass effect of the giant polycystic kidneys, the patient had been referred for a staged bilateral nephrectomy. During surgical planning, the option of concomitant adrenalectomy for PA if found to be unilateral, was reconsidered. The massive renal cysts grossly distorted normal retroperitoneal anatomy, making it impossible to identify the adrenal glands by either CT or MRI. Additionally, the complex anatomy made adrenal vein sampling both extremely difficult and risky.

In a multidisciplinary team meeting, the decision was made to perform an 131I-iodo-cholesterol scan (NP-59), which demonstrated a unilateral radiotracer accumulation in the left adrenal. Subsequently, a left adrenalectomy and nephrectomy was performed, resulting in rapid normalization of potassium levels and improvement of blood-pressure control. Spironolactone and doxazosin were discontinued. Pathology evaluation identified a 3cm adrenocortical adenoma.

Conclusion: 131I-Iodo-cholesterol scintigraphy is a useful modality for lateralization of PA and should not be disregarded. It could be used in selected cases, especially when adrenal venous sampling is contraindicated.





Thyroglobulin is a Poor Predictor of Differentiated Thyroid Cancer in Patients Operated for Thyroid Nodular Diseases

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Background:
Thyroglobulin, serves as a specific tumor marker following thyroidectomy in differentiated thyroid cancer (DTC) patients. However, its role as DTC predictor in patients with thyroid nodules (TN) is controversial.

Aim:
We aimed to assess the potential role of preoperative serum thyroglobulin concentration to predict DTC in patients who were operated for thyroid nodular disease.

Methods:
This retrospective study included patients who had partial or total thyroidectomy between January 2014 and May 2019, with preoperative diagnosis of benign multinodular goiter (MNG) or a TN with indeterminate cytology (INC; Bethesda system 3/4 categories). We compared patients for demographic, clinical, imaging, and biochemical data according to their final diagnosis: DTC or benign TN disease. Further statistical analysis included odds ratios calculation and receiver-operator curves (ROC) analysis.

Results:
Of 131 patients who met inclusion and exclusion criteria, the indication for surgery was benign MNG in 69, and TN with INC in 62 patients. Final diagnosis of DTC was reported in 18/69 (26%) and 30/62 (48%) of patients with preoperative diagnosis of benign MNG and INC-TN, respectively. Preoperative Median thyroglobulin was 148.5 ng/mL (IQR 67.8-1158.5) vs. 190 ng/mL (IQR 62.4-574), in malignant and benign MNG respectively (p= 0.97), and 160.5 ng/mL (IQR=82.2-536.7) vs. 205.5 ng/mL (IQR= 65.2-821.5) in malignant and benign INC-TN respectively (p= 0.93). Nodule diameter, TSH level, and thyroglobulin did not differ between patients with final diagnosis of DTC versus those with benign histology.

Conclusion:
Preoperative serum thyroglobulin alone is insufficient to differentiate preoperatively between malignant and benign thyroid disease.

Adrenal Venous Sampling for Diagnosis of Primary Hyperaldosteronism

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Background:

Primary Hyperaldosteronism is caused by overproduction of aldosterone in one or both adrenal glands. According to international guidelines, patients over 40 years old should have adrenal venous sampling (AVS) to distinguish between bilateral and unilateral disease. The aim of this study was to investigate the learning curve and safety of AVS, as well as advantages and pitfalls of the procedure.

Methods:

A retrospective study was performed on all AVS procedures done in Shaare-Zedek Medical-Center. Data collection included pre-procedure clinical information, adrenal imaging, AVS results and follow up. AVS protocol and interpretation of results were done according to International guidelines.

Results:

Since 2018, 25 AVS procedures were done for 24 patients. Mean age 54.1±9y, 20/25(80%) males. In 20/25(80%) the procedure was fully successful, with improvement over time, from 68% for the first twelve to 92% for the last twelve. In 5/25(20%) there was inability to locate the right adrenal vein; in four of whom lateralization was demonstrated by contralateral suppression. Overall 24/25(96%) had a conclusive result. In 10/24(42%) adrenal imaging was not accurate in confirming lateralization. No complications were observed. 12/17 patients with confirmed lateralization had unilateral adrenalectomy; all of them became normotensive with fewer or no medications for hypertension.

Conclusion:

AVS is a safe and efficient procedure and learning curve can be achieved after 12 cases. This series had a 96% conclusive lateralization result. With the known limitations of adrenal imaging to locate hyperaldosteronism source, AVS is a critical step in the management of primary hyperaldosteronism.

CDKN2A and CDKN2B Co-deletion Enhances Ammonia Metabolism in PDAC Liver Metastasis

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Background:
Liver metastases are often the direct cause of death of pancreatic ductal adenocarcinoma (PDAC) patients. We recently found, through analysis of 17,000 primary and metastatic PDAC samples, that deletion of CDKN2A and CDKN2B (encoding p15/p16 respectively) was more prevalent in liver metastasis compared to primary or other metastases sites. We also found that p15/p16 deletion enabled growth in liver environment. The liver environment is characterized by high ammonia levels, and we hypothesized that p15/p16-deletion confers growth advantage under these conditions.

Aim:
Reveal the mechanism p15/p16-deletion enables PDAC growth in liver conditions.

Methods:
PDAC cells, COLO357, PANC-1 and MIA PaCa-2, were either p15/p16 silenced or co-overexpressed. Transcriptomic was conducted with RNAseq. cJun pathway was studied by qRT-PCR, western-blot and gene-reported assay.

Results:
Transcriptomic analysis revealed enrichment in ammonia-associated gene pathway, especially GLUL up-regulation, leading to increased ammonia assimilation. Consequently, p15/p16 deleted cells grow better in high ammonia levels. GLUL promoter contains cJun binding sites, and transcriptomic analysis revealed elevated cJun expression in p15/p16-deleted cells. p15/p16 deletion led to activation of the cJUN pathway evidenced by JNK and cJun phosphorylation, cJun expression, and cJun transactional activity. We studied expression of GLUL following JNK inhibition and found that JNK inhibition decreased GLUL expression specifically in p15/p16-deleted cells. The opposite was observed upon p15/p16 overexpression.

Conclusions:
These data indicate that p15/p16 deletion leads to altered ammonia metabolism through GLUL upregulation, mediated by the JNK-cJUN pathway. This may affect adaptation of PDAC cells in the liver. This may lead to novel therapeutic strategies for PDAC patients.

Hypoglycemia in Children: Clinical Experience of a Tertiary Care Center

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Introduction:
Hypoglycemia, an important cause of morbidity in children, is a challenging condition to diagnose and treat due to its heterogeneity.

Aim:
To describe the diagnoses and clinical characteristics of children with hypoglycemia referred to our clinic.

Methods:
This retrospective, single center study included 155 children (86 males, 0-18 years) diagnosed with hypoglycemia in 1992-2018, and followed at a tertiary care center. Clinical and laboratory data were reviewed and compared among groups according to their etiologic diagnoses and age at referral.

Results:
The cohort was divided by clinical diagnosis into six groups: ketotic hypoglycemia (KH) (n=45, 29.0%); congenital hyperinsulinemic hypoglycemia (CHH) (n=33, 21.2%); transient HH (n=28, 18.7%); metabolic disorder (n=16. 10.3%); systemic disease/syndrome (n=15, 9.7%), and hormone deficiencies (n=10, 6.4%). At diagnosis 58 (37.4%) were neonates, 23 (14.8%) infants, 59 (38%) 1-6 years, and 15 (9.7%) 6-18 years. The most common diagnoses were: transient HH (48.3%) and CHH (32.7%) in neonates; CHH (34.8%) and KH (17.4%) in infants; KH (62.7%), metabolic disorders (11.8%) and CHH (10.1%) in children 1-6 years; and similar frequencies of KH, metabolic disorders, hormone deficiencies, and insulinoma in children 6 years. Comparisons of groups by diagnosis showed some statistically significant differences, with overlap between groups.

Conclusions:
Hypoglycemia etiology is heterogeneous and varies among neonates, infants, and children. Work-up should be directed for each age group based on clinical, biochemical, and imaging findings combined with next generation sequencing target panels.

Zoledronic Acid (ZOL) Administered Sequential to Teriparatide might Promote a Deeper Suppression of Bone Resorption than ZOL Alone

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Background:
Bisphosphonate efficacy is alterated according to baseline bone turnover. Teriparatide promotes bone turnover, however, it is not known whether pretreatment with teriparatide influences bone turnover suppression induced by ZOL, thereby possibly affecting a preferred subsequent treatment timing.

Aim:
To evaluate the effect of ZOL on bone resorption suppression in a post-teriparatide versus first line scenario in osteoporotic patients.

Methods:
Patients treated with teriparatide followed by ZOL (TPT-ZOL) or with a single infusion of ZOL were retrospectively identified in a tertiary referral bone metabolism center database. Demographic, clinical, densitometric and laboratory data, including C-terminal-telopeptide-of-Type-I-Collagen (CTX) following ZOL treatment were compared between groups.

Results:
Twenty-six patients treated with TPT-ZOL and forty-one with ZOL were comparable in gender (92.3% vs 92.7% female, p=0.4) and age at ZOL administration (median [IQR]: 70.1 [63.6,77.5] vs 69.6 [64.2,76.2], p=0.6). Femoral neck T-scores, vitamin D levels and timing of CTX measurement post-ZOL (median [IQR]: 12.1 [11.0,13.1] vs 12.2 [11.3,15.8] months, p=0.6), were similar. CTX was significantly lower among patients in the TPT-ZOL group (median [IQR]: 142.1 [91.2,220.8] vs 184.2 [159.0,262.0] pg/ml, p=0.005). In a regression model controlling for age, body mass index, kidney function and timing of CTX measurement, pretreatment with TPT was a strong predictor of a CTX level lower than 150 pg/ml, following ZOL treatment (OR=5.6, 95% CI 1.6-22.4, p=0.009).

Conclusions:
ZOL administered sequential to teriparatide promotes a deeper decline in serum resorption marker than ZOL alone. It is possible that in a sequential treatment scenario, subsequent ZOL dosing interval should be modified accordingly.

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Head-to-Head Comparison of 18F-AIF-NOTA-Octreotide and 68Ga-DOTA-TATE PET/CT in Patients with Neuroendocrine Neoplasms

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Purpose:
18F-AIF-NOTA-octreotide (F-Oc) is a radiolabeled somatostatin analog and a potential alternative for 68Ga-DOTA-TATE (Ga-DT). We have compared physiological and pathological findings in F-Oc and Ga-DT PET/CT studies in patients with NEN.

Methods:
Normal biodistribution and pathological findings were compared using maximum standard uptake value (SUVmax). Tumor-to-liver ratio was calculated by dividing the SUVmax of tumor lesions by liver SUVmax. Data are expressed as mean ± SD. Differences were assessed using Wilcoxon signed-rank test.

Results:
The results of F-Oc and Ga-DT PET/CT studies of six patients with biopsy proven NEN (F=4, mean age: 61.7 years), performed within 14-228 days (mean 65 days) were analyzed. Ga-DT showed higher physiological uptake in the spleen, salivary glands, pituitary and liver and lower blood pool activity compared to F- Oc. Of 27 abnormal foci (19 liver, 2 pancreatic, 6 mesenteric) F-Oc identified 24 (88.9%), compared to 23 (85.2%) for Ga-DT. Four subcentimeter foci (one mesenteric, three liver) were not visualized with Ga-DT, whereas three subcentimeter foci (two liver, one pancreas) were not seen on F-Oc. SUVmax of 20 lesions detected in both studies was 12.8±7.9 and 16.1±12.2 for F-Oc and Ga-DT, respectively (p= 0.1) and tumor-to-liver ratio was 2.9±2.0 and 2.3±1.8 for F-Oc and Ga-DT, respectively (p=0.007).

Conclusion:
These preliminary data show good agreement between F-Oc and Ga-DT in patients with NEN with a significantly higher tumor-to-liver ratio obtained with F-Oc. The potential added clinical value of these findings needs to be further evaluated and will be assessed in the entire patient cohort.

Extreme Hypercalcemia due to Primary Hyperparathyroidism: A Look-back on over a Decade in a Tertiary Care Center

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Background:
Extreme hypercalcemia is an endocrine emergency. Given parathyroid hormone (PTH)-dependent cause, carcinoma should be suspected as a possible etiology. The prevalence of parathyroid carcinoma among patients presenting with extreme hypercalcemia is not well elucidated.

Aim:
Establish proportion of patients with parathyroid carcinoma among those presenting with severe hypercalcemia and compare clinical and laboratory features between benign and malignant etiologies.

Methods:
Admissions during 2009-2021 with serum calcium ≥14mg/dl were identified via MD-clone platform. Cases with PTH mid-reference range or serum creatinine 1.5 mg/dl were excluded. Clinical, biochemical, and histological data were retrieved.

Results:
Twenty-seven patients meeting an inclusion criteria were identified (44% males). Those constitutes 5.3% percent of severe hypercalcemia hospitalized during 2009-2021. Calcium level was 15.3±0.3 mg\dl and PTH level 461±66 pg\ml. Twenty patients (74%) were symptomatic (constipation, polyuria/polydipsia, change in mental status). Eleven (40%) had a precipitating event. Ten (37%) patients were referred due to abnormal laboratory. Twenty-one underwent parathyroidectomy, with pathology of adenoma/ hyperplasia in 19 and carcinoma in 2 cases. Long-term (up to 6 years) follow-up of 2 non-operated patients suggests benign etiology. Levels of PTH, calcium, albumin and creatinine, and radiographic characteristics were indistinguishable between etiologies. Age at presentation was 78 and 79 years for carcinoma compared with 57.6 years (19-82 years) in the adenoma\hyperplasia group.

Conclusions:
Benign parathyroid disease was the most common etiology of severe PTH-dependent hypercalcemia. Significant clinical or laboratory predictors distinguishing benign from malignant etiologies were not identified.

Sporadic and von Hippel-Lindau Disease-related Pancreatic Neuroendocrine Tumors Definitions are not Consistent between the Various Classification Criteria

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Background:
von Hipple-Lindau (VHL) disease comprises hemangioblastomas, renal cell carcinomas (RCC), pheochromocytomas, and pancreatic neuroendocrine tumors (PNET). Diagnosis is based International (two hemangioblastomas, one hemangioblastoma and one visceral lesion, or VHL family history and hemangioblastoma\visceral lesion) or Danish criteria (any two clinical manifestations, one clinical manifestation and family background of VHL\self-genetic diagnosis). PNET in VHL seems distinct from sporadic PNET, as most are non-functioning with lower grade and rate of metastases, yet head-to-head comparisons are scarce.

Aim:
Compare VHL-related and sporadic PNET and Internation vs Danish-based diagnosis of VHL.

Methods:
PNET cases identified via MDClone, data gathered included demographic, tumor-specific characteristics, and clinical features\genetic diagnosis\family background of VHL.

Results:
Twenty-nine patients with VHL (17 (58%) with PNET) and 65 with sporadic PNET were identified. PNET diagnosis age was younger for VHL compared with sporadic PNET (50.1±4.7 vs. 62.8±1.5 years, p0.001). There was no significant difference between VHL-related or sporadic PNET in stage, grade, progression, or survival.

Age at diagnosis of PNET, RCC, and VHL was younger in the International vs Danish group. Hemangioblastomas diagnosed in 90% of patients in the International vs none in the Danish. The first manifestation was hemangioblastomas (47%), then pheochromocytoma (31%) in the International, and RCC (62%) and PNET (37%) in the Danish group. Fifty percent had family\genetic background in the International and none in the Danish group.

Conclusions:
Diagnosis of VHL according to International or Danish criteria form two distinct clinical groups, with greater similarity of the Danish group to sporadic PNET patients.

Multiple Endocrine Neoplasia Type 4 (MEN4): Case Report and Review of Literature

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Background:

MEN4 is an autosomal dominant disorder caused by a germline CDKN1B mutation, characterized by the occurrence of hyperparathyroidism, pituitary adenomas, and neuroendocrine tumors (NET). Less than 60 MEN4 cases were described thus far.

Aim:

To describe a family harboring a pathogenic variant in CDKN1B and review the literature on MEN4 clinical course.

Methods:

A Pubmed search using the terms CDKN1B and MEN4.

Results:

Case report: A 40-year-old male with aortic root dilatation was referred to our clinic due to genetic workup for suspected Marfan syndrome yielding a CDKN1B variant (c.320delA, p.Q107fs). The patient`s medical history is negative otherwise. However, family history was positive of hyperparathyroidism (age 40) and aortic root dilatation in his father, and small intestine NET and hypercalcemia in his paternal grandmother. On Sanger sequencing of alive family members, the patient's father (72 y/o), asymptomatic son (6 y/o), sister (44 y/o), and her daughter (18) harbored the same CDKN1B variant.

Literature search yielded 23 case reports/series on MEN4, describing 60 patients (53 symptomatic, 29% males). The most frequent clinical manifestation was hyperparathyroidism (61.6%, median age at presentation 50 years [range 15-74])), pituitary adenoma (33.3%, age 12 years [5-62]) and NET (16.6%, age 50 years [35-69]), either variable presenting feature. Of note, hyperparathyroidism presented as either single or multiple adenomas.

Conclusions:

MEN4 is a rare syndrome with clinical presentation similar to MEN1 yet with a relatively late presentation of hyperparathyroidism and NET. In contrast, MEN4-related pituitary adenomas may present at an early age, possibly calling for earlier surveillance.

Post-Cushing's Syndrome Events: Remission is not Always the End of the Story

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Background:
While successful surgery for Cushing`s syndrome (CS) may lead to dramatic clinical improvement, associated morbidities may persist and adverse treatment effects may occur in remission.

Objective:
Describe the metabolic features and adverse treatment outcomes in patients with CS who achieved remission.

Methods:
Retrospective electronic charts-review of patients, insured at Maccabi Healthcare Services, who underwent successful surgery for non-malignant CS in 2005-2019 without evidence of recurrence.

Results:
The cohort included 100 patients (80 women, age 44.9±14); 55% with pituitary and 45% with adrenal CS. Mean weight reduction was 10.1±8.8kg following surgery, from 83.4±21.5kg at diagnosis (BMI 30.2±7.3kg/m2) to 72.5±20kg at 14.5±17.2 months post-surgery (BMI 26.4±6.2kg/m2) (p0.001).

Rates of hypertension and diabetes mellitus/impaired fasting glucose decreased from 54% and 40% at diagnosis, to 26% and 21% during remission, respectively (p0.001).

Surgical complications included prolonged/permanent diabetes insipidus in 6 patients and one case of panhypopituitarism.

Glucocorticoid-replacement therapy was administered to 96/100 patients for 25.1±43.4 months. Nine patients were admitted to emergency-room due to hypoadrenalism. Glucocorticoid-withdrawal symptoms, including poly-arthralgia, skin-rash and severe weakness, were recorded in 22/96 patients (22.9%).

Within the first post-surgical year, 9/100 patients experienced new/relapse of immune/allergic/steroid-responsive conditions, mainly arthritis and asthma/atopic-dermatitis. Three women were newly diagnosed with depression and 2 had exacerbation of depression. Psychosis was newly diagnosed in 2 women and fibromyalgia in 3 women.

Conclusions:
Significant weight-loss and metabolic improvement occur in remission of non-malignant CS. Yet, increased awareness to the risk of adverse "post-CS" outcomes in a significant percentage of patients may impact treatment decisions

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מלון ענבל, ירושלים

Impact of Basal Bolus Insulin Therapy on Glucose Control and Mortality in Patients with Type 2 Diabetes Hospitalized With COVID-19: A Retrospective Study

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Introduction:
Insulin is the mainstay of diabetes therapy in the inpatient setting. However, the treatment of diabetes in patients with COVID-19 remains unclear. In this study we investigate the influence of different insulin regimens and other antidiabetic medications on glucose control in COVID-19 patients with type 2 diabetes.

Methods:
We conducted a retrospective electronic medical record analysis of 359 type 2 diabetes patients hospitalized with COVID-19 in the Emek Medical Center. We divided the patients into two groups based on their diabetes treatment during hospitalization. The first group included patients treated only with insulin, and the second group of patients were treated with insulin and other classes of antidiabetic drugs

Results:
Of 359 patients, 82 were mechanically ventilated and 110 patients suffered a severe course of COVID-19. During hospitalization, most of the patients in the combination therapy group received metformin on top of insulin (131 out of 162, 80%), 28 patients (17%) received SGLT-2 inhibitors, 12 (7%) were treated with DPP-IV or GLP-1 agonists. Average blood glucose was higher in patients treated only with insulin 192±69 mg/dl versus 169± 59 in the second group (p=0.003). HbA1C levels improved after hospitalization in both groups of treatment, and overall: A1C levels before admission were 7.9±1.9 mg% and after 7.5±1.7 mg% (P=0.002).

Conclusion:
Our study shows that new antidiabetic medications, such as incretin-based therapy and SGLT-2i, as well as metformin in combination with insulin may be safe, and effectively control glucose levels in hospitalized COVID-19 patients with type 2 diabetes.

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Does the Risk of New Metabolic Changes among Thyroid Cancer Survivors Depend upon Thyroid Function?

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Background:
Various components of metabolic syndrome (MS) are known to significantly increase the risk of thyroid cancer (TC). Moreover, thyroid cancer survivors (TCS) are at increased risk of de novo components of MS. The role of thyroid function (TF) in this context has not yet been determined.

Aim:
To investigate changes in selected MSC and their association with TF during a two-year follow-up among TCS.

Methods:
This retrospective, nested case-control study used data from a single academic hospital. The one-hundred and fifteen participants had undergone total thyroidectomy and radioactive iodine treatment, followed by thyroid stimulating hormone supressive L-thyroxine therapy for two years due to differentiated TC.

Results:
The incidence of MS and its components increased in 51 TCS (cases) during a two-year follow-up. The other 64 TCS (controls) did not develop any new components of MS during the same period. The multivariable logistic regression analysis showed that TCS with a FT3/FT4 ratio greater than 0.22 (lower tertile) had a significantly increased risk of a new MSC (odds ratio 2.73, 95% confidence interval 1.14-6.57, p=0.025).

Conclusions:
This study demonstrated that an FT3/FT4 ratio greater than 0.22 is correlated with detrimental metabolic changes among TCS.

Central Neck Recurrence after Unilateral versus Bilateral Level 6 Dissection in Patients with Papillary Thyroid Carcinoma

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Background:
Surgery for papillary thyroid cancer (PTC) often includes prophylactic or therapeutic lymph node dissection of the central neck compartment. Controversy exists regarding the extent of dissection, whether unilateral or bilateral, and its influence on disease recurrence rates.

Aim:
To assess disease recurrence rate in the central neck on the contralateral side among patients undergoing total thyroidectomy and central neck dissection.

Methods:
A retrospective study on patients diagnosed with PTC who underwent total thyroidectomy and central neck dissection between 2006-2021, and were followed in Rabin Medical Center, Israel. Patients were divided to two groups according to the type of surgery - unilateral or bilateral central neck dissection. The primary end point was the disease recurrence rate in central neck on the contralateral side.

Results:
We included 81 patients (69%female) with a mean age of 45 years (range 21-89). 27 patients (33%) underwent bilateral central neck dissection and 54 patients (67%) unilateral central neck dissection. The disease recurrence rate in the central neck was 0% and 3% for unilateral vs. bilateral central neck dissection. The disease recurrence rate in the lateral neck was 7% for both groups. Permanent vocal cord paralysis was seen in 2 patients (2.5%), both underwent bilateral central neck dissection. Hypoparathyroidism was seen in 2 vs. 5 patients among unilateral and bilateral central neck dissection, respectively.

Conclusions:
Our study demonstrates comparable disease recurrence rates for patients who underwent unilateral versus bilateral central neck dissection. Moreover, we found a higher complication rate among patients undergoing bilateral central neck dissection.

The Effect of Front of Package Labeling on Food Sales in Israel

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Background:
Front-of-package labelling (FOPL) of unhealthy foods and beverages is a strategy thought to reduce consumption of unhealthy foods and halt the soaring rates of non-communicable diseases. It is one of the policy strategies recommended by the World Health Organization and was implemented in Israel in January 2020. There is limited evidence for the effectiveness of FOPL.

Aim:
To assess whether products that were marked as unhealthy by FOPL had lower sales compared to unlabeled products.

Methods:
Longitudinal data on sales of packaged foods and beverages in large food retails throughout Israel was analyzed. Differences in sales between summer 2019, and summer 2020 were calculated. The association between the unhealthy FOPL compared to non-labelling and the difference in sales was assessed in three food categories using a multivariate linear regression model. Additional covariates included geographical area, number of unhealthy labels, price changes, and products targeting children.

Results:
Data on labelling status and sales during both studied periods of time was available for 384 items in the cereals category, 401 items in non-alcoholic beverages category, and 1444 items in the dairy category, representing 83%, 60% and 90% of the market, respectively. In multivariate analysis, unhealthy FOPL was not a predictor of changes in sales between the studied periods.

Conclusions:
Unhealthy FOPL was not associated with reduced sales compared with unlabeled food products. Limitations: FOPL was implemented early in the COVID-19 pandemic, which may have blunted its effect on consumer food choices. This analysis did not assess FOPL effect on basket composition.

Patients' Preferences Regarding Telemedicine in a Multidisciplinary Clinic for Type 1 Diabetes following the COVID-19 Pandemic

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Background:
The COVID-19 pandemic brought to light both challenges and unique opportunities regarding type 1 diabetes (T1D) management including usage of telemedicine platforms. Between March and June 2020 during the period of the first lockdown, remote medicine almost completely replaced conventional visits. After that patients could choose how to conduct visits whether frontally or remotely.

Methods:
The study was conducted in the diabetes clinic at Kaplan Medical Center. All consecutive T1D patients during March and June 2021 were asked to fill a structured anonymous questionnaire which aimed to evaluate patients` perceptions, desires, and limitations regarding continuous use of a virtual platform.

Results:
126 T1D patients answered the questionnaire, of whom 51% were under the age of forty, half were men, half used insulin pumps and 69% continuous glucose monitors. During the pandemic, the exposure of patients to virtual visits has grown about two-fold, from 29 % to 53%. Forty-nine percent expressed an interest in future usage of a virtual platform, but most of them in a hybrid manner. We found an association between preference to use telemedicine in the future and younger age, previous virtual platform experience and confidence in being able to download data.

Conclusions:
Our data demonstrate that the COVID-19 experience led to a growing interest of T1D patients in using the hybrid format of telemedicine. However, we still need to better understand who will benefit mostly from this platform and assess its` cost-effectiveness and organization.

Breastfeeding Rates in Pre-gestational Diabetes – Where Do We Stand?

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Background:
Data suggests that women with pre gestational diabetes mellitus (PGDM) tend to breastfeed less compared to women without diabetes. We aimed to evaluate any or exclusive breastfeeding (BF) rates at three and six months in PGDM and whether targeted counseling at the end of pregnancy can impact breastfeeding rates and duration.

Methods:
Fifty-two women with PGDM were cluster randomized between 32-36 weeks gestation, either to frontal instruction (FI) with a BF counselor or elaborated written information on BF with diabetes (non-frontal instruction, NFI). 38 women without diabetes giving birth at our center served as controls. All women filled a questionnaire regarding BF duration and intensity before instruction, and at three and six months after birth.

Results:
Twenty-six women completed the questionnaire in each group. 63% had type 1 diabetes and the rest had type 2 diabetes. Women in the NFI were younger (31±5 vs 35±5 years) and more likely to have higher education. Past BF rates were similar and almost all women in our cohort intended to breastfeed. At three- and six-months postpartum, any BF rates were around 60% and 30%, respectively. Approximately half of those breastfed exclusively in each group. No difference was noted between FI and NFI.

Conclusions:
BF rates in PGDM were comparable to those of women without diabetes. Mode of instruction did not confer a difference in BF rates or duration. Although results are encouraging continuous education and support are required.

A Unilateral Large Adrenal Tumor First Identified during Pregnancy: A Diagnostic and Therapeutic Dilemma

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Introduction:
Adrenal non-adenomatous tumors (NAT) first identified during pregnancy are very rare and pose a diagnostic and therapeutic dilemma with significant risks for the mother and fetus.

Aim:
To report a case of a large adrenal NAT identified in pregnancy and literature review.

Methods:
A literature search conducted, and data summarized.

Case Presentation:
A 37-year-old primigravida women, with a history of melanoma excised 12 years prior to presentation without recurrence, presented at 35 weeks′ gestation due to intractable right flank pain. MRI demonstrated an eight cm, heterogeneous, septate, right adrenal mass suspected to be either pheochromocytoma, adrenocortical carcinoma (ACC) or metastasis. Blood metanephrines were sent urgently to enable a safe delivery and were within normal range, as were cortisol and androgen levels. A day later she delivered by cesarean section. PET CT done after delivery revealed extensive metastatic spread of recurring melanoma including the adrenal.

The most commonly reported adrenal NAT in pregnancy is Pheochromocytoma. Most were secreting with leading symptoms of hypertension, palpitations and headaches. All women needed medical treatment prior delivery. Significant maternal morbidity exists despite treatment. A few case reports identified ACC first recognized during pregnancy. The leading presentation was Cushing`s. Maternal and fetal prognosis is poor. A few case reports identified metastasis from breast and lung cancers. None reported adrenal metastatic melanoma.

Conclusions:
Timely diagnosis and management by a multidisciplinary team are important to avoid a catastrophic outcome. There is no consensus on optimal management and timing of delivery. Pheochromocytoma should be ruled out before delivery.

Fine-Needle Aspiration of Parathyroid Lesions Prior to Parathyroidectomy: A Tertiary Center Experience

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Aim:
Parathyroid lesion aspiration as a preoperative adenoma localization tool is a matter of controversy. Concerns are being raised regarding both the immediate (hematoma, infection, histologic alterations) and long term (seeding) safety.

Our study aims to evaluate the safety and efficacy of the procedure.

Methods:
We retrospectively reviewed all parathyroid FNA procedures performed in a tertiary referral center between 2011 and 2021. Clinical, biochemical, and imaging information as well as cytology, surgery, and pathology reports were extracted from electronic medical records.

Results:
Twenty-nine hyperparathyroid patients referred to parathyroidectomy following a positive localization with FNA -PTH washout were available for review. The main indications for aspiration were re-confirmation of location, mismatch between imaging modalities and intra-thyroid lesions.

No immediate procedure complications except for mild neck discomfort were documented.

Among 24 patients with an available pathology report, parathyroid adenoma was identified in 22, non-adenomatous parathyroid tissue in one and thyroid tissue in one patient.

No cases of hematoma or abscesses were reported by the surgeons, and no histologic alternations (hemorrhage, abscess, inflammation or capsule rupture) were reported by the pathologists. There was one case of necrosis and one case of adenoma with fibrotic changes that may or may not be related to the FNA.

Twenty-six (89.6%) of the 29 patients who underwent parathyroidectomy, were biochemically cured up to a follow-up of 41.6±34.6 months.

Conclusions:
Parathyroid FNA with PTH washout was accurate and neither immediate nor surgical or preparate-related complications were demonstrated in our series. This approach might be considered in selected cases.

Endo - Genetic Clinic as a Tool for Better Clinical Yield in Genetic Evaluation of Endocrine Cases

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Introduction:
Endocrinopathies may have a genetic origin. Identification of the genetic basis of endocrine diseases can shorten the workup process and ameliorate therapy. There is paucity in data regarding the potential effects of integrated clinic in which both endocrinology and genetics specialists see the patient together.

Aim:
Evaluation of endo-genetic clinic impact amongst endocrine patients, on the rate of genetic etiology diagnosis.

Methods:
This is a retrospective trial, of endocrine patients consulted by endo-genetic clinic in Carmel Medical center during 2017-2021.

Results:
During 5 years 210 participants were seen in the endo-genetic clinic. This group had a higher yield of genetic diagnosis compared to the yield of the genetic clinic (20% vs 10%).

Conclusions:
Amongst endocrine patients, endo-genetic clinic is associated with higher genetic diagnosis rate. Further research is needed to assess endo-genetic clinic effect on larger scale data.

Diabetes Mellitus (DM) is Associated with Poor Outcome in Pembrolizumab-treated Non-small Cell Lung Cancer (NSCLC) Patients

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Introduction:
Pembrolizumab and other Immune check-point inhibitors became the mainstay of treatment in ample malignancies, including NSCLC. Though DM causes immune dysfunction, the effect of DM on the efficacy of immunotherapy has not been addressed.

Methods:
Medical records of consecutive NSCLC patients treated with first-line pembrolizumab alone or combined with chemotherapy at Tel Aviv Medical Center from January 2017 to July 2021 were reviewed. We excluded patients who received a single cycle or were lost to follow-up.

Results:
Of 234 patients reviewed, 203 were included in the analysis. Their median age was 69 years, 128 were men (63%), 152 had adenocarcinoma (75%), and 51 patients had DM (25%). Diabetic patients were older (73 vs. 67, p 0.001) and had a higher mean body mass index (27 vs. 24, P0.001). Median progression free survival (PFS) and overall survival (OS) were significantly shorter in diabetic compared to non-diabetic patients (5.9 vs. 7.1 months, respectively, P=0.004, and OS 12 vs. 21 months, respectively, p=0.006). The difference in OS was more pronounced for patients receiving pembrolizumab alone (12 vs. 27 months, p=0.03), than for those receiving pembrolizumab together with chemotherapy (14.3 vs. 19.4 months, p=0.06). Multivariate analysis indicated DM as an independent risk factor for inferior PFS (HR 1.7, 95% CI 1.11-2.5, p=0.014) and OS (HR 1.7, 95% CI 1.09-2.76, p=0.02).

Conclusions:
Here we show a potential deleterious effect of DM on the efficacy of pembrolizumab in metastatic NSCLC patients. If further validated, the administration of single agent pembrolizumab in this setting should be reconsidered.

Hypocalcemia as the Initial Presentation of Type 2 Bartter Syndrome: A Family Report

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Bartter syndrome (BS) is a group of rare autosomal-recessive tubulopathies characterized by hypokalemic, hypochloremic metabolic alkalosis in which the primary defect is a deficiency of transporters involved in sodium chloride reabsorption. Type 2 BS results from a defect in the renal outer medullary potassium channel encoded by the KCNJ1 gene. Type 2 BS presents with polyhydramnios, intrauterine growth retardation, prematurity, failure to thrive, polyuria, hypercalciuria, and life-threatening episodes of dehydration. Hypocalcemia is a very rare presenting symptom of BS, with only a few published cases reporting it as the initial manifestation of type 2 BS.

Aim:
To describe a child who presented with hypocalcemic seizure at the age of 2.3 years that was first related to vitamin D deficiency and high-phosphate soft drink consumption.

Methods:
Whole exome sequencing (WES) was used to evaluate the biochemical abnormalities of the proband.

Results:
We identified a previously described homozygous missense mutation c.212CT, p.T71M in the KCNJ1 gene associated with type 2 BS. Six additional family members with the same mutation and diagnosed clinically with BS are also reported, two presenting with hypocalcemia associated with vitamin D deficiency

Conclusion:
This report expands the clinical spectrum associated with KCNJ1 mutations and emphasizes the role of WES in unsolved cases of hypocalcemia when genetic disease is suspected. It also highlights the hazardous effects of phosphate-containing soft drinks on calcium metabolism.

Reactive Oxygen Species in the Development of Gonadal Failure in Late-Onset Transaldolase Deficiency

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Background:

Transaldolase is an enzyme regulating NADPH and ribose 5-phosphate production in the pentose phosphate pathway (PPP). Previously 39 patients with transaldolase deficiency have been described. The presenting symptoms are hepato(spleno)megalia, anemia, thrombocytopenia, dysmorphic facial features, abnormal skin, cardiac abnormalities, intra uterine growth restriction and hypergonadotropic hypogonadism. Liver failure is the main cause of mortality. The mechanism causing hypogonadism is not fully understood. The TALDO1 gene is highly expressed in steroidogenic cells. There could be a combined effect of damage to the steroidogenic cells having a high demand for NADPH for steroidogenesis and regulation of reactive oxygen species (ROS), and toxic effects of intermediate metabolites of the PPP.

Clinical case:

A 15y male was referred to our clinic due to absence of pubertal development. He was known to have atrial septal defect, renal tubulopathy, dysmorphic facial features and transient elevation of liver enzymes. Lab results showed hypergonadotropic hypogonadism. Parents were of Jewish Indian heritage. Whole exome sequencing showed homozygosity for a novel T167M missense mutation in the TALDO1 gene. Both parents were heterozygote for this mutation. Fibroblasts from the patient showed an increased production of ROS, indicating an increased susceptibility to oxidative stress, and suggesting a possible effect of antioxidant treatment.

Conclusion:

This case demonstrates in vitro increase of ROS in cells with PPP defect due to transaldolase deficiency, presenting clinically with hypergonadotropic hypogonadism and atrial septal defect. Cellular damage due to high ROS levels is thus indicated as a possible mechanism for gonadal failure in transaldolase deficiency patients.

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מלון ענבל, ירושלים

The Interplay between Excess Weight, Socioeconomic Status, and Risk for SARS-CoV-2 Infection

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Introduction:
Multiple studies show a high proportion of obesity among confirmed cases of SARS-CoV-2 infection and recent studies have suggested higher rates of infection in low socio-economic status (SES). The interplay between SES and obesity as risk factors for infection is unknown.

Aim:
Our goal was to investigate the interaction between obesity and SES as risk factors for SARS-CoV-2 susceptibility when the alpha variant was dominant.

Methods:
We designed a cross-sectional study of subjects with available BMI measurements and a SARS-CoV-2 PCR test results, presenting to the emergency department at the Sheba Medical Center between March 16 and November 15 2020.

Results:
The odds of testing positive for SARS-CoV-2 in subjects with overweight (BMI 25.0-29.9 kg/m2) as compared to subjects with normal weight (BMI 18.5-24.9 kg/m2) were significantly higher (OR = 1.46, 95% CI 1.12 - 1.92) and this relationship remained significant after adjusting for age, gender, SES and population density. For every 1-unit increment in SES, the odds for positive test results decreased by 0.83 (95% CI: 0.78-0.88). In addition, we found that the probability of testing positive for SARS-CoV-2 with every 1 kg/m2 increment in BMI was significantly higher only for subjects of low SES after adjusting for the above confounders.

Conclusion:
Our analysis shows the interplay between excess weight and sociodemographic measures where higher BMI did not increase the risk for SARS-CoV-2 infection in high SES groups, but when superimposed on low-SES it was associated with a markedly increased risk.

Deciphering Liver Glycome Regulation by the PGC-1/FN3K Axis

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Introduction:
Diabetes in general, and specifically in the context of obesity, is characterized by hyperglycemia resulting in non-enzymatic glycation of proteins. Yet, the full scope of molecular targets for glycation, particularly in liver, is incompletely understood. De-glycation, which removes the attached sugars, is controlled intracellularly by fructosamine-3-kinase (FN3K). However, whether intracellular de-glycation is regulated in physiological contexts and what factors are involved in its regulation remain unknown.

Aim:
To identify factors controlling the regulation of FN3K and protein glycation in liver.

Methods:
Gene expression analysis in mouse liver and cell culture experiments with overexpression of the key metabolic regulators PGC-1s (PGC-1α and PGC-1β). Mass spectrometric analysis was used to monitor protein glycation.

Results:
Our data identify that regulation of protein glycation in liver is controlled by the key metabolic regulators PGC-1s in response to metabolic cues, particularly in the fed state. Liver-specific deletion of PGC-1s results in reduction of Fn3k expression and concomitant increase in specific protein glycation. In accordance, overexpression of PGC-1α in liver-derived cells induces Fn3k and reduction in protein glycation. Purification of glycated proteins followed by mass spectrometric analysis and subsequent validations reveal significant alterations in intracellular protein glycation in response to PGC-1α expression. Mechanistically, PGC-1α effect on Fn3k involves the activity of the transcription factor Foxo1.

Conclusions:
In liver, fasting and re-feeding govern intracellular protein glycation via PGC-1 dependent induction of FN3K. Our work reveals the scope and dynamic nature of the liver glycome, establishing the PGC1/FN3K axis as a key regulator of protein glycation.

PEDF As a Possible Marker for Early Onset of Reproductive Aging

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Introduction:
Aging has a detrimental effect on the female reproductive system, manifested by deteriorated fertility parameters as hampered oocyte quality and poor embryo development. Our previous work established the anti-oxidative potential of a multipotential protein, Pigment epithelium-derived factor (PEDF) in alleviating oxidative damage in granulosa cells (GCs) of both women and mice, and oocytes in mouse model.

Aim:
To elucidate the involvement of PEDF in ovarian aging.

Methods:
Using young and reproductively aged ("aged") mice, ($n \geq 19$), we analyzed: (1) Relative mRNA expression of PEDF, VEGF, AMH and FSHR in GCs; (2) in vitro matured oocytes' (IVM) rate; (3) oocytes' ATP content± rPEDF (5nM). Furthermore, we collected GCs and follicular fluids (FF) from young and aged patients undergoing IVF, ($n \geq 10$) and performed similar qPCR analysis, and determined by ELIZA PEDF protein level in GCs and FF.

Results:
rPEDF significantly improved oocytes' IVM rate of aged compared to young mice whereas the level of ATP and mtDNA remained similar. The level of PEDF mRNA was significantly higher in GCs of aged mice and women, compared to that of young controls, with no significant changes in the expression level of VEGF, AMH or FSHR mRNA. However, in aged women, the level of PEDF protein in both GCs and in FF, was significantly lower, with no change in PEDF secretion ratio pointing on translational problem.

Conclusions:
Our findings demonstrate the involvement of PEDF in early stages of ovarian aging leading us to suggest PEDF as a possible marker for early onset of reproductive aging.

Preoperative Diagnosis Impact on Surgical Strategies and Outcomes in Patients with Medullary Thyroid Carcinoma

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Introduction:
Due to the difficulties with cytological identification of medullary thyroid carcinoma (MTC), the correct diagnosis is obtained postoperatively in a significant subset of patients.

Aim:
To investigate the impact of preoperative MTC misdiagnosis on management and outcomes.

Methods:
Retrospective series of MTC patients treated at three tertiary referral centers in Israel from January 2000 to June 2021. The included patients were grouped and compared based on the presence or absence of preoperative MTC diagnosis.

Results:
Ninety-four patients with histopathologically confirmed MTC were included (mean age 56.2±14.3 years, 43% males), of whom 41 (44%) were diagnosed with MTC postoperatively (i-MTC group), and 53 (56%) had preoperative MTC diagnosis (d-MTC group). The extent of surgery, including completion procedures, was as follows: total thyroidectomy in 82% vs. 100%, central lymph node dissection (LND) in 46% vs. 98%, ipsilateral lateral LND in 36% vs. 79%, and contralateral lateral LND in 17% vs. 28% of i-MTC vs. d-MTC patients, respectively. Histopathology revealed a median tumor size of 16±17.4 mm vs. 23±14.0 mm, the proportion of micro-MTC [size ≤ 10 mm] 31.7% vs. 15.1%, in i-MTC vs. d-MTC groups, respectively. Biochemical cure, defined as undetectable calcitonin at 3 months postoperatively, was reached in 57% of i-MTC patients vs. 64% of d-MTC patients (p=0.53). After exclusion of patients with micro-MTC, the biochemical cure was achieved in 37% vs. 62% (p=0.04) of i-MTC vs. d-MTC patients, respectively.

Conclusion:
Preoperative MTC misdiagnosis remains a relevant clinical scenario that may result in suboptimal surgical management and lower curative rates.

QTc Prolongation in Transgender Female Adolescents Receiving Gonadotropin-releasing Hormone Agonist: Preliminary Data

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Background:
The QT interval corrected for heart rate (QTc) is used as a marker of ventricular arrhythmia risk. Testosterone has a shortening effect on QTc length, and the QTc interval in cisgender males is shorter than in females. Transfemale adolescents are treated with GnRH agonists (GnRHa) that suppress testosterone secretion and might prolong the QT interval and increase the risk for arrhythmia.

Aim:
To analyze QTc interval in transfemale adolescents before and after receiving GnRHa and after estrogen treatment.

Methods:
In this prospective study QTc was analyzed in transfemales who started treatment at Tanner stage 4/5, before and after GnRHa treatment and after adding estrogen. QTc was measured using the Hodges formula to correct for heart rate. Prolonged QTc was considered 450 ms.

Results:
Twenty transfemales were include .QTc in the 10 participants that initiated GNRHa alone was significantly prolonged compared to baseline (381.9±17.71 vs 404.48±22.19 ms,respectively,p=0.015), but did not increase450 ms. Of these 10 participants, 7 continued to estrogen treatment. QTc was observed to increase after GnRHa treatment and decrease back after adding estrogen treatment (386.4±19.8 vs 413.7±19.9 vs 402.0±23.5 ms,respectively, p=0.05). QTc did not increase significantly in 17 participants treated with both GNRHa and estrogen compared to baseline.

Conclusion:
QTc interval may prolong after GnRHa treatment in Tanner 4-5 transfemales adolescents, while estrogen and GnRHa combined treatment may not affect QTc. This may be of concern, as incidence of mental health conditions requiring psychopharmacotherapy is high in transgender youth, with many psychiatric medications known to prolong the QT.

Elevated Levels of ACTH in a Patient on High Doses of Steroids Treatment: Pitfalls in Steroid Sandwich Immunoassays

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Introduction:
Accuracy in hormonal testing is necessary in endocrine practice. However, false positive laboratory results can obscure the correct diagnoses.

Aim:
To report the case of falsely elevated ACTH in a young man treated with steroids.

Methods:
Investigate true ACTH levels through analysis of the presence of heterophile and/or nonspecific antibodies.

Case Presentation:
A 18 year- old man was admitted for the investigation of high cortisol and ACTH levels despite high doses of prednisone treatment for autoimmune hepatitis. Medical history and physical examination did not elicit findings of hypercortisolism. Due to lack of response to treatment, noncompliance was suspected. Hypothalamic-pituitary- adrenal axis (HPA) was examined, and the following results were obtained: ACTH level 22 pmol/L (2.2-11.0) and cortisol level 359 nmol/L (119-618 nmol/L). Other pituitary hormonal axes were normal. Levels of renin, aldosterone, DHEA-S, total testosterone, SHBG and androstenedione in the normal range excluded the option of partial glucocorticoid resistance. Interference in ACTH assay was suspected (Immulie 1000 – Simenes), and elimination of nonspecific antibodies was done using Non Specific Antibody Blocking Tube (NABT- Scantibodies). As a result, a low level of ACTH, less than 2.2nmol/l was found in concordance with steroid treatment. Regarding the relatively high cortisol levels, 34% cross-reactivity with prednisone was detected by Siemens (Centaur), analytical platform.

Conclusion:
Interpretation of endocrine testing should always be done in conjunction with clinical assessment of the patient, history of associated diseases, and concomitant medications. Any discrepancy between clinical and laboratory data should raise the suspicion of pitfalls in hormonal immunoassays.

High Estradiol Levels in Postmenopausal Women- Pitfalls in Laboratory Diagnosis

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Introduction: Ovarian estradiol secretion ceases at menopause and is followed by very low levels of circulating estradiol generating typical menopausal symptoms.

Aim: To report a case of false high estradiol levels in a postmenopausal woman

Methods: Assessing true estradiol levels by neutralizing the effect of heterophile and/or nonspecific antibodies and by using an alternative analytical platform.

Case presentation: A 67-year-old woman was seen at an endocrinology clinic with high serum estradiol levels of 603 pmol/l in repeat tests and typical postmenopausal symptoms. She underwent multiple imaging studies including fluorodeoxyglucose -positron emission tomography scan and brain MRI in an attempt to identify the source of estradiol secretion. Adnexectomy revealed normal histopathology. After surgery, detected estradiol levels were as high as before. Postmenopausal levels of serum LH, FSH, DHEA-S and androstenedione were found. We suspected that our patient's high estradiol was due to interference in the assay (Centuar – Simenes). Checking with two other methods (Cobas-Roche and Access-Beckman Coulter), showed estradiol results less than the detection limit in both analyzers typical to postmenopausal estradiol levels. An estradiol result of 110 pmol/l after blocking heterophile antibodies (HBT -Scantibodies), proved the presence of heterophile antibodies which caused interference to the estradiol assay of Centaur- Simenes.

Conclusions: This case demonstrated that false elevated estradiol measurements in postmenopausal woman could be caused by presence of heterophile antibodies interfering with the accuracy of investigations. Exclusion of method-specific bias or interferences of the test system is required if clinical symptoms are not in line with the detected hormone levels.

Pregnancy and Lactation Induced Qsteoporosis: A Social-Media Based Survey

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Background:

Pregnancy and lactation induced osteoporosis (PLO) presenting as spinal fractures is rare. The spectrum of clinical presentation, risk factors and pathophysiology are incompletely understood.

Aim:

To delineate clinical parameters in women with PLO, and to compare risk factors and osteoporosis-related quality of life with a control group.

Methods:

Participants of a social-media (WhatsApp) PLO group were offered a questionnaire, including osteoporosis-related quality of life section (MINI OQLQ). Mothers of young children in parent WhatsApp groups were approached to serve as random controls.

Results:

Twenty-four patients with PLO and 43 controls (36.9±4.8vs38.8±4.3y.o.,p=0.11) replied. More than 5 vertebrae were involved in 50%, 4 in 25% and 3 or less in 25%. 85.7% of the fractures were a-traumatic. Nineteen percent of the fractures occurred during pregnancy and others, during early postpartum period. Diagnosis was delayed for over 16 weeks in 41.8% of women. 62.5% received teriparatide. A significantly lower proportion of women in the PLO group engaged in physical activity over 2 hours/week during pregnancy (37.5vs86.3%,p0.05). Seventy-one percent of the PLO patients expressed fear of fractures and 58.3% fear of falls compared to none and 2.3%, respectively (p0.01) of the controls.

Conclusions:

PLO-related spinal fractures involve multiple vertebrae in the majority of the affected women, and the diagnosis is delayed. Less physical activity might pose a risk. Most of PLO patients in our cohort were treated with teriparatide. PLO patients reported a significant impairment of quality of life. Multidisciplinary effort should be exerted to early identification and treatment of this severe condition.

Immunotherapy Induced Glycemic Dysregulation – Characterization and Proposed Mechanisms Beyond Beta-Bell Autoimmunity

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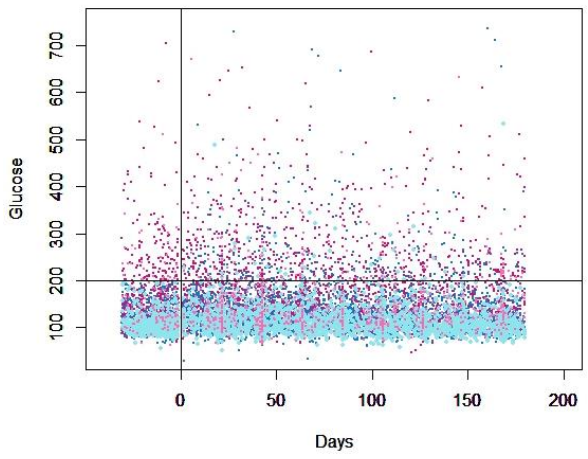
Aim:

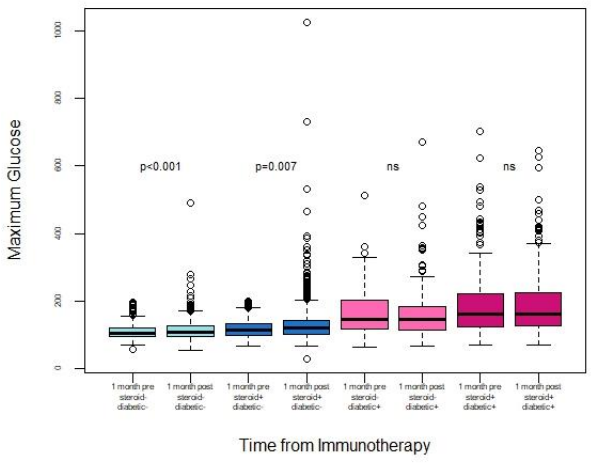
Immunotherapy has revolutionized cancer treatment while introducing a new spectrum of immune-related adverse effects (irAE). Hyperglycemia is frequently observed after initiation of immunotherapy. Immune-mediated type 1 diabetes mellitus, currently the only defined condition, represents only a minority of cases (estimated prevalence 0.5%). We aimed to characterize dynamics and effectors of glycemic dysregulation following immunotherapy.

Methods: A retrospective study, using the MD-Clone interface to retrieve electronic medical data of all cancer patients treated with immunotherapy during the years 2015-2021.

Results: Among 3384 patients, a statistically significant increase in glucose levels was observed after initiation of immunotherapy [mean of maximum 132.3mg/dl ± 55.8 vs 139.8 ± 64.6 (p-value0.001)]. Glycemic dysregulation was significant in non-diabetic patients [n=2549, mean of maximum 109.6 mg/dl ±22.9 vs 114.3 mg/dl ±31.4, p0.001], and was aggravated by glucocorticoids (anti-emesis for chemo-immunotherapy protocols or for irAEs [118mg/dl ±26.2 vs 130.6 mg/dl ±53.2 p0.007]. Diabetic patients, though, presenting with significantly higher glucose levels and wider variability, both aggravated by glucocorticoid therapy, had no significant increase in glucose levels after initiating immunotherapy.

Immunotherapy induces a significant glycemic dysregulation among non-diabetic cancer patients, assumingly via an increase in insulin resistance resulting from cytokine flare and systemic inflammation. This effect is assumingly concealed among diabetic patients, in whom multiple baseline distorted mechanisms are involved in glycemic dysregulation. The possibility of a distinct, reversible, autoimmune damage to beta cells would require evaluation in a prospective study with a dynamic assessment of the beta-cell reserve.





Body Composition Measurement by Bioimpedance: A Simple Tool or Tailoring Gender-affirming Care in Transgender Adolescents

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Background:
In transgender adolescents, estrogen and testosterone dose are based on weight and body surface area (BSA) respectively. Testosterone requirements in transmales are associated with increased BMI, whereas, in transfemales the effect of BMI on estradiol dose requirements is inconclusive. Body composition assessment may provide a more nuanced approach to customize gender-affirming hormone care.

Aim:
To explore the relationship between body composition parameters and hormone levels in transgender adolescents on gender-affirming hormone therapy.

Methods:
Seventy-nine transgender adolescents (54 transmales) treated in the Israeli Pediatric Gender Clinic. Body composition was assessed by bioelectrical impedance analysis (BIA, Tanita MC-780 MA). Outcome measures: estradiol and testosterone levels in correlation with indices of adiposity (total/truncal fat percentage) and muscle (muscle-to-fat ratio).

Results:
Weight distribution differed between genders (p=0.002) with a greater proportion of underweight in transfemales (32% vs 3.7%) and a greater proportion of overweight/obese in transmales (31.5% vs 20%). Testosterone peak levels in transmales were negatively correlated with total and truncal fat percentage (r=-0.48 and r=-0.41 p0.05,respectively) sarcopenic index (r=-0.58,p0.01) and BSA (r=-0.62,p0.01) and positively correlated with muscle-to-fat ratio z-score (r=0.33,p=0.03). Testosterone through levels negatively correlated with sarcopenic index (r=-0.35,p=0.017) and BSA (r=-0.28,p=0.028). In transgender females, estradiol levels did not significantly correlate with body composition parameters.

Conclusion:
Body fat and the balance between muscle and fat, as demonstrated by BIA, correlates with testosterone peak levels in transmale adolescents on gender-affirming treatment and may help dose adjustment. This is of importance as weight status and body composition varies greatly in this population.

Cannabinoids and the Endocannabinoid System as Modulatory Targets in Neuroendocrine Neoplasms (NENs) – Possible Mechanisms and Antitumor Efficacy

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Introduction:
Patients with unresectable NENs are offered a variety of non-curable therapeutic options, which eventually fail due to drug resistance (DR). Increasing evidence suggest an anticancer trait of cannabinoids, via cellular pathways including mTOR, known to be associated with DR development. Still, limited data exist on the anti-cancer effects of cannabinoids in NENs.

Aims:
To understand the possible anti-tumor role of the cannabinoids and the endocannabinoid system in NENs, and their ability to overcome resistance to everolimus (Eve).

Materials and Methods: The endocannabinoid receptors (ER) expression on NENs cell lines of lung (NCI-H727) and pancreatic (BON1) origin and on human samples was examined using FACS/immunofluorescence staining and RNA-Seq. Cells were treated with multiple cannabinoids extracts (CE). Viability and apoptosis were examined using WST-1 and Annexin/PI. ER blocking with specific antagonists examined CE-induced toxicity. The effect of Eve ± CE/ER-antagonists on cell viability was examined.

Results:
The ER CB1, but not CB2, is highly expressed in NEN cell lines and tumor samples. The expression of other ER (TRPV1, TRPV2, PPARα and PPARγ) is heterogeneous. 50 CE were initially tested, identifying 6 CE that significantly reduced cell viability by ~40% via CB1. Also, CB1 blocking vigorously decreased cells viability and increased apoptosis. Cells viability decreased by 15% with Eve alone; this effect was enhanced when CE and mainly CB1 antagonists were added (by 33% and 59%, respectively).

Conclusions:
Modulation of endocannabinoid system seems promising in NENs models, mostly via the ER CB1. Addition of CE/CB1 antagonist to Eve may have synergistic effects, with possible important therapeutic impact.

Availability of Levothyroxine Formulations Impacts the Use of Thyroid Hormones: A THESIS Questionnaire Survey of Israeli Endocrinologists

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Background:

Treatment of hypothyroidism is available in several formulations, including tablets, soft-gel capsules, liquid, as well as LT3 formulations.

Methods:

Israeli Endocrine Society (IES) members were invited to participate in the international incentive THESIS (Treatment of Hypothyroidism in Europe by Specialists: An International Survey).

Results:

A total of 123 physicians participated in the survey, with 65.1% women, 65.1% aged 41 to 60 years old, and 92.7% had more than 10 years in practice. LT4 tablets are used as first line therapy by 99.2% of respondents. Formulations prescribed include tablets by 100%, soft-gel capsules by 4%, liquid solution by 15.4%, compounded LT4 by 2.4%, and LT3 by 17.8%. In cases of impaired absorption (drugs or GI conditions) or inadequate control of hypothyroidism, most would continue LT4 tablets (86.1%-95.1%), of whom 36.6%-39% noted that only tablets are available in Israel. Only 4.9%-9% would prescribe other formulations. In comparison, in Italy were other formulations are readily available, soft-gel capsules would be prescribed by 29.7%-32% and liquid solution by 45.7%-66.9%. In patients with normal TSH and persistent symptoms, 95.1% would continue LT4 tablets (compared to 57.1% in Italy, 87.5% in Denmark, 75.4% in Romania). LT4/LT3 combination would be considered by 57.5%, whereas 24.4% stated this combination should never be used.

Conclusions:

In Israel, LT4 tablet formulation is the treatment of choice in most clinical scenarios, including in patients with impaired absorption or persistent symptoms. Other formulations, which are not widely available, are infrequently used compared with other European countries.

The Adipokine FABP4 – A Key Regulator of Neonatal Glucose Homeostasis

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During pregnancy, fetal glucose production is suppressed, with rapid activation immediately post-partum. Fatty acid-binding protein 4 (FABP4) was recently demonstrated as a regulator of hepatic glucose production and systemic metabolism in animal models.

Aims:
To evaluate FABP4's role in regulating neonatal glucose hemostasis.

Methods:
Serum samples were collected from pregnant women with normoglycemia or gestational diabetes at term, from the umbilical circulation, and from the newborns within 6 hours of life. The direct impact of FABP4 on glucose homeostasis was studied by injection of recombinant FABP4 to Fabp4-knockout (Fabp4-/-) neonates. Mice neonatal liver were also subjected to transcriptome analysis.

Results:
FABP4 level was higher in the fetal vs. maternal circulation with a further rise in neonates after birth by ~3-fold. Neonatal FABP4 inversely correlated with blood glucose with ~10-fold increase in hypoglycemic neonates. When studied in mice, blood glucose of 12hr-old wild-type, Fabp4-/+ and Fabp4-/- littermate mice was 59±13 ng/dL, 50±11 mg/dL and 43±11 mg/dL, respectively (p0.05). Similar to our observations in humans, FABP4 levels in wild-type mice neonates was ~8-fold higher compared to adult mice. RNA-Seq of neonatal liver suggested altered expression of multiple glucagon-regulated pathways in Fabp4-/- mice. Indeed, Fabp4-/- liver glycogen was inappropriately intact, despite a significant hypoglycemia, with rapid restoration of normoglycemia upon injection of recombinant FABP4.

Conclusions:
Our results highlight the importance of FABP4 as a significant factor in regulating post-natal systemic glucose metabolism, as part of the orchestrated hormonal and metabolic adaptive response to maintain glucose homeostasis in the immediate post-natal period.

The Role of Adipocyte Connexin-43 in Mediating Adipose Tissue Inflammation and Dysfunction in Obesity

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Introduction:
Obesity is a leading global health concern and a major risk factor for type-2 diabetes. Thus, identifying mechanisms linking obesity to insulin resistance is of great importance. Chronic low-grade inflammation of the adipose tissue (AT) has been shown as an important pathophysiological link between obesity and the development of systemic insulin resistance. Gap junction (GJ) intercellular-communication, primarily composed of connexin-(Cx)43, has recently been reported to have immunomodulatory roles in various tissues, with increased Cx43 expression and GJ activity implicated in the response of various tissues to chronic stress.

Aim:
To study the role of Cx43 in shaping the AT adaptive or maladaptive response to the cellular insults of obesity.

Methods:
We have used a diet-induced obesity (DIO) mouse model to study the effect of obesity on Cx43 expression and the role of Cx43 in the AT response to obesity, by using wild-type (WT) and adipocyte-specific Cx43 knock-out (AdCx43KO) mice.

Results:
DIO resulted in increased AT Cx43 expression, primarily attributed to increased Cx43 expression in adipocytes. In AdCx43KO mice, we observed increased macrophage infiltration to the AT as compared to WT mice, accompanied by morphologic changes in the AT and increased variability in adipocyte size. While AdCx43KO mice did not significantly differ from WT mice in body weight, adiposity or food intake, they demonstrated reduced whole-body insulin sensitivity assessed by insulin tolerance test. Mechanistically, we observed that adipocytes can interact directly with neighboring adipocytes and macrophages via Cx43-composed GJ.

Conclusions:
Our results suggest an immunomodulatory role for adipocyte-Cx43 in obesity.

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Clinical Correlates of A Large Israeli Cohort of Cys 618 Arg RET Mutation

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Introduction:
A MEN2A syndrome with Hirschsprung`s disease described in Israeli Jews of Moroccan descent is caused by Cys 618 Arg mutation. We aimed to define characteristics of a large cohort with this mutation from a multi-center Israeli registry.

Methods:
The Israeli multi-center MTC registry was searched for patients with Cys 618 Arg mutations.

Results:
Fifty-three patients (19.3%) had documented RET mutations; 29/53 (54.7%) had the Cys 618 Arg mutation. Through development of a family tree spanning five generations, a familial connection was determined for 28/29 patients, descendants of one family of Moroccan Jewish descent. Another 4 patients from the MTC registry without available genetic test results belonged to this family. Clinical data of these 32 patients was analyzed.

Nineteen patients (59%) were female. Age at surgery was 26.6 ±12.8 years. Tumor size was 10.8 ±9.3mm. Extrathyroidal extension was described in 4/19 (21.0%); vascular invasion in 5/18 (27.8%); multifocality in 17/21 (81.0%) and bilateral lesions in 17/22 (77.3%). Lymph node metastases were found in 3; distant metastases in 3.

Surveillance duration was 9.3 ±12.9 years. Recurrence occurred in 4/19 patients (21.2%), 3 with distant metastases. Seven patients had additional therapy: 4 surgery, 2 radiotherapy and 1 tyrosine kinase-inhibitors. Two patients died during follow-up; one death was disease-related. Two patients had pheochromocytoma, 2 had Hirschsprung disease and 1 had primary hyperparathyroidism.

Conclusion:
The prevalent RET mutation in Israel is Cys 618 Arg; almost all cases were linked to one large family of Moroccan descent. Comorbidities included pheochromocytoma and hyperparathyroidism, rendering screening essential.

Stress Vulnerability Increases the Severity of Obesity-induced Metabolic Alterations in HFD-fed Mice

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Introduction:
Obesity is a risk factor for development of cardio-metabolic disease, however a high metabolic heterogeneity exists among individuals with the same BMI, ranging between a subgroup of highly-affected subjects (metabolically unhealthy obese, MUO) to those who are considered as metabolically healthy obese (MHO). The exact mechanisms affecting the metabolic health of obese subjects have not yet been discovered.

Objective:
To clarify whether differences in stress response determine the metabolic health of obese mice. Methods: The study was performed in a mouse model of social dominance (Dom) and submissiveness (Sub) which also relates to differing levels of stress sensitivity. Mice were given high fat diet (HFD) or standard diet (STD) for 8 weeks, followed by physiological, histological and molecular analyses.

Results:
Obesity was developed in both groups, however HFD-feeding induced hyperleptinemia and a severe glucose intolerance and insulin resistance in Sub mice, while Dom mice were almost unaffected. Histochemistry analysis revealed pancreatic islets hypertrophy and pancreatic steatosis in Sub mice, with a lower severity of such pathologies in Dom mice. In addition, Dom mice were protected from HFD-induced hepatic steatosis, which was observed in Sub mice. Adipocyte hypertrophy and altered expression of adipocytokines was observed in STD-fed Sub mice, suggesting that stress vulnerability lead to dysfunction of adipose tissue.

Conclusions:
Stress vulnerability increases the risk to develop MUO. Mapping the protective mechanisms that promote MHO is important for the development of treatment strategies to reduce the risk for obesity-associated comorbidity diseases in obese individuals.

Patients' Adherence and Satisfaction from Daily Versus Monthly Vitamin D Supplementation: Results from a Dedicated Bone Clinic

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Introduction:
Monthly vitamin D supplementation is not inferior to daily regarding target vitamin D levels and might increase adherence. Patients` adherence and satisfaction with daily versus monthly vitamin D supplementation have been hardly investigated.

Aim:
To evaluate patients with osteopenia/osteoporosis regarding adherence and satisfaction from vitamin D supplementation after switching from monthly to daily (MtD) dosing and vice versa (DtM).

Methods:
Ambulatory osteopenic/osteoporotic patients were asked to switch their vitamin D supplementation from MtD and vice versa. Total monthly dose remained unchanged. Patients answered questionnaires regarding socio-demographics, medical status, compliance with vitamin D dosing (MMAS-8), satisfaction with regimen and physical functional status (OPAQ-15) at baseline and 6 months after switching.

Results:
Among 72 patients recruited (71.5±7.4Y, 91.7%F), 52(72.2%) were switched from DtM treatment, 20(27.7%) from MtD. Baseline vitamin D level was 86.1±17.2 nmol/l. Both groups expressed good baseline compliance (MMAS-8 score ≥8; 98.1%) and good baseline satisfaction (~75%) with vitamin D regimen. Baseline physical status was good in 63.9% and moderate in 33.3%. After switching, satisfaction level, adherence to vitamin D regimen, vitamin D level and functional capacity remained unchanged. 68.8% of MtD and 52% of DtM patients wanted to remain on the current regimen. Among patients who experienced both regimens, 56.1% preferred the daily one.

Conclusions:
Patients with osteopenia/osteoporosis had good adherence to monthly/daily vitamin D regimens and expressed high level of satisfaction with them. All parameters remained stable after switching regimens. Large-scale studies are needed to evaluate the effects of various dosing regimens on patients` satisfaction and adherence.

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Insulin Degrading Enzyme (IDE) and Physical Function in Elderly Adults with Diabetes Mellitus

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Background:
IDE was suggested to play an important role in maintaining blood insulin levels. Sofer et al 2021 suggests a correlation between elevated levels IDE in the serum of metabolic syndrome, pre diabetes, to C peptide.

Aim:
To examine the association between serum IDE levels and physical indices in elderly adults with diabetes mellitus type 2 (DM2).

Methods:
A cross sectional study that included 91 individuals with diabetes over the age of 60. Demographics, medical history were collected. In addition, participants underwent assessment of physical capacity using validated tests of aerobic, balance and strength capacity conducted by a licensed physiotherapist. Serum IDE levels were determined using a highly sensitive ELISA. Participants were divided into above and below median IDE level and the difference in study variables distribution between the two groups was determined using the Mann-Whitney test.

Results:
Those with IDE levels above and below the median IDE levels did not differ significantly in age, gender, diabetes duration, diabetes complications, dyslipidemia or hypertension prevalence, A1c% or insulin usage. Those with IDE levels above the 50th percentile exhibited better performance in a variety of physical function tests including the 6-minute walking test (513 vs 458 meter; P=0.012), 30 seconds chair stand (14.5 vs 14; P=0.005) and grip strength (32 vs 25 kg; P=0.026).

Conclusions:
Higher IDE levels in patients were associated with better performance in physical capacity tests. This may suggest that IDE may represent an important marker for insulin activity to follow during disease progression.

Immunohistochemical Staining of E-cadherin is Inversely Correlated with the Presence of Metastases of Papillary Thyroid Carcinoma

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Background:
Papillary thyroid carcinoma (PTC) is the most common type of primary thyroid cancer with a low incidence of distant metastases. A few studies have explored the correlation between immunohistochemical staining of PTC and risk of tumor metastases and extrathyroidal extension (ETE).

Aim:
To evaluate the correlation between the intensity of different immunohistochemical marker staining in PTC and the risk for extrathyroidal extension or metastases.

Methods:
The study included patients who underwent complete or partial thyroidectomy for PTC at Bnai-Zion Medical Center. Thyroid tissues were immunohistochemically stained for different tumor proliferative markers: Minichromosome maintenance protein 2 (MCM2), Ki-67 labeling index, E-Cadherin, Neuropilin-1 and Metallothionein. The correlation between the intensity of each staining and tumor extrathyroidal extension and metastases were evaluated.

Results:
The study included 44 patients: 21 patients with thyroid confined PTC who had neither ETE nor metastases, 12 patients with PTC with ETE without known metastases, and 11 PTC patients who had cervical lymph nodes metastases or distant metastases. No staining correlated with extrathyroidal extension. The intensity of E-Cadherin staining was significantly lower in PTCs with metastases than thyroid confined PTCs and PTCs with extrathyroidal extension (P 0.028 and 0.021, respectively). The intensity of the staining of the immunohistochemical markers: MCM2, Neuropilin-1 and Metallothionein did not correlate with presence of metastases. Ki-67 nuclear staining was significantly lower in PTCs with ETE than PTCs with metastases, however it did not significantly differentiate between thyroid confined tumors and metastatic ones.

Conclusions:
Immunohistochemical staining of E-Cadherin significantly and inversely correlated with the presence of metastases of papillary thyroid carcinoma.

Sensitivity of Different ACTH and Cortisol Concentration Values in Corticotropin-releasing Hormone-based Tests in Cushing`s Disease

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Background:
Despite a set of multiple diagnostic tests, Cushing`s syndrome usually poses a diagnostic challenge.

Aim:
To determine sensitivity of several ACTH and cortisol concentration values in different time points in patients with Cushing`s disease (CD), during corticotropin-releasing hormone (CRH) stimulation test and during CRH stimulation following dexamethasone suppression (DEX-CRH) test.

Methods:
We retrospectively analyzed cortisol and ACTH concentration increment during CRH and DEX-CRH tests in 23 patients with confirmed CD. Cortisol and ACTH concentrations were determined immediately before, 15 minutes and 30 minutes after CRH stimulation. We evaluated the sensitivity of different cutoff values including those reported in previous studies, in the diagnosis of CD.

Results:
During DEX–CRH test, 15 minutes serum cortisol concentration of 1.4 µg/dl (38 nmol/L) had a sensitivity of 90.9% for a diagnosis, and serum cortisol concentration ≥ 1.27 µg/dl (35 nmol/L) had a sensitivity of 100%. For plasma ACTH, sensitivity of 100% was obtained using ACTH ≥ 3.5 pmol/L (16 pg/ml) at 30 minutes.
During CRH test, 35% increase in ACTH concentration 15 minutes after stimulation had a sensitivity of 72.72% for a diagnosis. While, 20% increase in cortisol 30 minutes after stimulation yielded a sensitivity of 85.7%. The best sensitivity of ACTH and cortisol increment was obtained 15 minutes after stimulation, using 19% and 9% increase, respectively (sensitivity of 100% and 92.85%, respectively).

Conclusions:
During CRH and DEX-CRH tests, the study findings agree with the good sensitivity of ACTH and cortisol cutoff values suggested in previous studies; yet, other cutoff values may give a higher diagnostic sensitivity.

Thyroidectomy on VA-ECMO for Thyroid Storm: A Case Report

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Introduction:

Thyroid-storm with heart-failure is a rare, life threatening complication of hyperthyroidism. In refractory cases, urgent thyroidectomy is required for definitive control of thyrotoxicosis. Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO) is a supportive measure for cardiorespiratory failure requiring continuous anticoagulation to prevent clotting. Here, we present a case of thyrotoxic cardiac-failure, successfully treated with thyroidectomy while on VA-ECMO. To our knowledge, only one such case has previously been reported.

Case:

A 48-year-old women with a known history of poorly controlled Graves` disease and resulting heart-failure with reduced ejection-fraction, was admitted for vomiting and rapid atrial-fibrillation. Initial treatment for suspected thyroid-storm included propranolol, propylthiouracil, Lugol`s solution and hydrocortisone. Soon-after, the patient suffered cardiorespiratory collapse with refractory cardiogenic shock requiring implantation of an Intra-aortic balloon-pump and VA-ECMO for circulatory support. Laboratory thyrotoxicosis was confirmed and daily plasmapheresis was added, though multi-organ failure ensued. Urgent thyroidectomy was deemed necessary to definitively control thyrotoxicosis but weaning from ECMO seemed impossible. In a joint multidisciplinary decision including endocrinology, cardiology, cardiothoracic-surgery, ENT, hematology, MICU and anesthesiology, anticoagulation was withheld for 24-hours to allow for surgery on ECMO. Total thyroidectomy with meticulous hemostasis was uneventful with preservation of recurrent nerves and parathyroids. Penrose drains were placed to secure gradual resumption of anticoagulation. Thyrotoxicosis resolved and ECMO was explanted with normalization of cardiac function. Due to severe ICU myopathy patient was eventually discharged to a rehabilitation facility.

Conclusion:

Urgent thyroidectomy for treatment of thyroid-storm is a viable option even on VA-ECMO. A multidisciplinary team-based approach is critical for success.

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Predicting Toxicity of Peptide Receptor Radionuclide Therapy (PRRT) in Patients with Somatostatin Receptor-positive Metastatic Neuroendocrine Tumors Treated with 177Lu-dotatate

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Introduction:
Peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE is considered the most efficacious intervention for patients with metastatic well-differentiated neuroendocrine tumors expressing somatostatin receptors. The aim of this study was to identify toxicity susceptibility markers, for hematologic, renal and hepatic toxicities.

Methods:
This was a retrospective cohort study. Data were obtained from Sheba Medical Center electronic database. Patients were treated with 177Lu-DOTATATE based on the NETTER-1 protocol and multidisciplinary team discussion. Serial blood tests were recorded for complete blood count, liver and kidney function tests before each PRRT cycle (baseline), 2-4 weeks post-cycle, and at last follow-up.

Results:
Twenty-four patients were included, 14 (58.3%) men. Three patients received chemotherapy before PRRT. Baseline leukocytes and platelets counts decreased over the four treatment PRRT cycles (Kruskal-Wallis, p

Conclusion:
177Lu-DOTATATE is associated with increased liver tissue vulnerability and kidney damage reflected by early hyperfiltration. 1st cycle changes may serve as markers for overall bone marrow and kidney toxicity.

Appendiceal Neuroendocrine Neoplasms diagnosed during Pregnancy-Case Series and Review of the Literature

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Introduction:
Although appendicitis occurs in approximately 1:1000 pregnancies, appendiceal neuroendocrine neoplasm (ANEN) diagnosis during pregnancy is very rare. Data on presentation, treatment and prognosis is scarce.

Aim:
To describe ANEN cases diagnosed during pregnancy.

Materials and Methods a retrospective appraisal of 7 consecutive ANEN patients diagnosed during pregnancy from four Israeli tertiary medical centers and comparison with 17 cases described in the literature from 1965-2021.

Results:
Age at ANEN diagnosis was 26.4±3.5 years (range 21-33). Patients were diagnosed between gestational weeks 6-40, most frequently in the third trimester (53%). The most common presenting symptom was abdominal pain.

Tumor size was 14.3±8.9mm (range 3-45mm). In patients from our series appendiceal base involvement was reported in 2/7; mesoappendiceal invasion in 5/7; lympho-vascular invasion in 2/7. KI-67 staining was reported in 6/7 cases and ranged from 1-10%. Pathology details were lacking in most of the previously published cases.

All 7 pregnancies in our series resulted in term delivery with no complications, whereas in historical cases there were one first trimester abortion, one ectopic pregnancy, and one stillbirth.

Right hemicolectomy was performed in 5/7 patients in our series and reported in 2/17 historical cases. All hemicolectomies were performed after delivery, 3-16 months after appendectomy. Local metastases were reported in two cases. Follow-up duration was 7-98 months in our patients and 3-48 months in 5 previous cases. No disease recurrence, distant metastases or mortality were noted.

Conclusions:
ANEN diagnosis during pregnancy is extremely rare. Pregnancy outcomes were usually favorable and long-term prognosis was excellent.

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The Long Way to a SHORT Syndrome: A Case Report from the Endocrine-Genetics Clinic

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Introduction:
The field of Endocrinology has witnessed a rapid expansion in the taxonomy of monogenic disorders. The following presentation of a rare diagnosis illustrates the complexity of the endocrine genetics field.

Case description:
A 37-year-old patient underwent thyroidectomy and radioiodine treatment due to Papillary thyroid carcinoma. A debilitating myalgia necessitating chronic opioid treatment emerged, with no known etiology despite an extensive evaluation.

Medical History:
Thyroiditis, Dyslipidemia, speech delay, delayed dentition, myopia, diabetes-adult onset, hypogonadism, hearing impairment.

Physical Exam:
Central obesity, short stature (153cm), temporal wasting, gynecomastia

Genetic evaluation:
Muscular disorders gene panel– Negative.

Whole Exome Sequencing (WES) in trio during his daughter`s pregnancy (due to IUGR and shortening of long bones) - Negative.

Revision Analysis of WES Raw Data:
The patient and his daughter were detected with a Heterozygous *PIK3R1* c.1712TC, p.Ile571Thr likely pathogenic variant

Discussion:
Pathogenic variants in the gene *PIK3R1* are associated with SHORT syndrome. This syndrome manifests as IUGR, short stature, partial lipodystrophy, insulin resistance, hearing loss and dental issues. An association between pathogenic variants in *PIK3R1* and thyroid carcinoma, has been suggested. We present a familial case of the patient and his daughter, that are clinically consistent with SHORT syndrome diagnosis.

Though myalgia is reported as a rare chronic complication of radioiodine treatment, it might be triggered by lipodystrophy.

A molecular diagnosis of SHORT syndrome provides the etiological explanation for this enigmatic manifestation, it explains a multitude of manifestations in the patient and its progeny, influences their follow-up and treatment, and has implications for future pregnancies.

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Comparison of Physical Function and Physical Activity between Above and Below Recommended Glucose Target Range in Older People with Type 2 Diabetes

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Introduction:
Physical activity (PA) is reported to be important for blood glucose management and overall health. Individuals with diabetes are encouraged to engage in exercise and to increase their total daily PA. Continuous glucose monitoring (CGM) identifies an individual's current glycemic status and provides valuable information about the amount of time spent in the recommended glucose target range (70-180 mg/dL), defined as Time in Range% (TIR). In this study we aimed to compare the physical function (PF) and PA between individuals with a lower and higher TIR.

Methods:
Twenty participants were recruited at "The Center for Successful Aging with Diabetes", Sheba Medical Center. They underwent PF tests including the 6-minute walk test (6MW) to asses aerobic capacity and the Sit-to-Stand test (STS) to asses leg strength. They were connected to a CGM system (I Pro2 carelink, Medtronic) and wore an activity device (ActiGraph GT9X) for a week. Number of steps, sedentary and light to vigorous activity time were recorded. Individuals were divided into 2 groups according to the TIR% obtained from the CGM (70% and ≤70%), all outcome measurements were compared between the groups.

Results:
The 70%TIR group demonstrated significant (p=0.04) higher performance on the STS test and trend towards statistical significance (p=0.07) on the 6MW. No significant differences were found between the groups in the number of steps, and time in sedentary, light to vigorous activity.

Discussion:
Participants with higher %TIR performed better in functional tests, however their daily PA was no different from the group with lower %TIR.

Evaluation of the Emotional and Cognitive Effects of Hormone Therapy in Transgenders

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Background:
Sex hormones are known by having far-reaching effects on the nervous system and the brain, both emotionally and cognitively. Studies have found a connection between varying levels of different types of sex hormones and changes in emotional states and cognitional abilities. However, most studies have dealt with the effects of adding a deficient hormone, or examining a single functional aspect, most often in cross-sectional studies.

Aim:
In this longitudinal study, we attempted to evaluate the effect of hormone therapy on cognition (memory, attention, and executive functions) and emotional state (depression and anxiety) in transgender men and women.

Methods:
The study involved 16 transgender men and women who began hormone therapy to gender adjustment at the Endocrine Institute at Ichilov Medical Center. Among the participants were 5 transgender men who have been treated with testosterone, and 11 transgender women who have been treated with estrogen and antiandrogen therapy. The participants completed mood self-report questionnaires and a cognitive diagnosis was transferred to them Before the beginning of hormone therapy, and 3-6 months after.

Results:
In both transgender men and women, the executive function measure before the beginning of hormone therapy was significantly lower than the measure with hormone therapy The difference in the measures of memory, attention and emotional stress was not found to be significant.

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High Prevalence of Acromegaly in Different Industrial Areas: A Population-based Study at Haifa and Western Galilee District – Clalit Medical Health Care

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Objective:
National registries for acromegaly and population-based data have an important contribution to disease understanding and management. Data concerning the epidemiology of acromegaly in Israel is scanty.

Design:
The epidemiology of acromegaly was studied in different industrial areas in northern Israel

Methods:
Data from adult patients diagnosed with acromegaly in 2000-2020, living in Haifa and Western Galilee District were collected using the electronic database from Clalit Medical Healthcare. Additionally, medical records were reviewed carefully. The prevalence of acromegaly in three distinct areas and overall were reported. Additionally, other epidemiological data including associated comorbidities, pituitary tumor size and treatment modalities were collected.

Results:
77 patients with a confirmed diagnosis of acromegaly were identified. The overall prevalence was 155 cases/ 106 inhabitants without statistically significant differences between the three areas. The mean age at diagnosis was 50 ±1.8 years and the male to female ratio was 1.1. Macroadenoma and microadenoma were identified in 44 (57%) and 25 (33%) respectively. The frequency rate of acromegaly-associated comorbidities such as diabetes, hypertension, carpal tunnel syndrome and osteoporosis was similar to previously reported studies. The mean BMI was 29 ± 5.6 kg/m2 and obesity with a BMI ≥ of 30 kg/m 2 was found in 29 (38%) of the patients. The majority of patients underwent transsphenoidal surgery 67 (87%), normalized IGF-1 was reported in 64 (83%).

Conclusion:
High prevalence of acromegaly was found in northern Israel. The pituitary microadenoma frequency rate is the Highest to be reported.

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