sanofi

Presents

AACE
ANNUAL MEETING
May 12-14, 2022

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGY

ANNUAL MEETING 2022

DAILY COVERAGE

TOP 7 SESSIONS: DAY-3

TOPIC OF CONTENT

SESSION-1: ADDRESSING THE UNMET NEEDS OF PATIENTS ON MULTIPLE DAILY INJECTIONS OF INSULIN SPONSORED BY BIGFOOT BIOMEDICAL

ADMINISTERING NUTRITIONAL INSULIN POSTPRANDIALLY IN THE INPATIENT SETTING IS ASSOCIATED WITH IMPROVED GLYCEMIC METRICS

Saturday, 14th May 2022

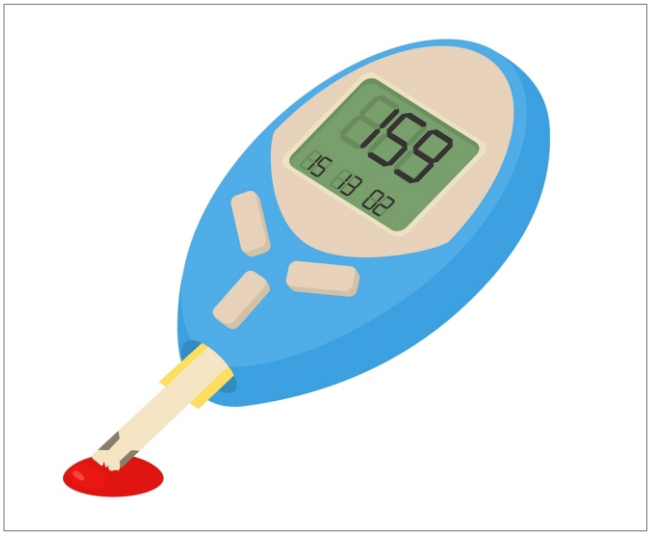
This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr. Andrew P. Demidowich, MD from Johns Hopkins Medicine.

In many hospitals, as in the outpatient setting, nutritional (i.e., rapid-acting) insulin is typically injected before the meal. However, hospitalized patients frequently have poor oral intake due to their acute illness. Nurses must often guess whether to administer or withhold a patient's preprandial insulin, depending on whether they feel the patient will eat. Guessing incorrectly can be deleterious, as administering insulin without food intake may result in hypoglycemia, while conversely holding insulin unnecessarily can lead to hyperglycemia. The objective of this study was to evaluate whether implementation of a hospital policy to deliver nutritional insulin postprandially, as compared to pre-prandially, was associated with changes in inpatient glycemic metrics.

This was a retrospective cohort study performed at Howard County General Hospital, a member of Johns Hopkins Medicine, using a de-identified data set. In June 2019, hospital policy shifted the timing of all nutritional insulin to be given after at least 50% of the meal was consumed, instead of pre-prandially. Because a full-time endocrine hospitalist was hired to consult on all inpatients with diabetes in August 2018, we restricted the data set to compare the nine months pre-policy (September 2018 to May 2019) vs. nine months post-policy implementation (July 2019 to March 2020). Patients who received at least one unit of insulin and had a glucose measurement were included in the analysis. Primary outcome was the rate of inpatient hypoglycemia, as defined by a glucose ≤70 mg/dL. Secondary outcomes included rates of moderate hypoglycemia (<54 mg/dL), severe hypoglycemia (≤40 mg/dL), hyperglycemia (mean daily glucose ≥180mg/dL), length of stay (LOS), and 30-day readmission rates (30DRR). Chi-square with Yates' correction or Student's t-test were used to analyze the differences between groups.

Rates of hypoglycemia significantly decreased from 5.9% (592 of 10,023 patient-days) to 5.0% (500 of 9,987 patient-days) post-intervention ($p=0.006$). Hyperglycemia rates also significantly decreased post-intervention (45.7% vs 42.5%; $p<0.0001$). Rates of moderate (1.9% vs 2.1%; $p=0.23$) and severe hypoglycemia (0.6% vs 0.6%; $p=0.98$) were not significantly different between groups. LOS and 30DRR were not significantly affected.

Our study found that administering nutritional insulin post-prandially, instead of pre-meal, in



the inpatient setting significantly decreased rates of hypoglycemia as well as hyperglycemia. Further study is warranted to evaluate whether this dosing strategy impacts patient experience or nursing comfort/distress regarding insulin dosing and inpatient diabetes.

RECURRENT FASTING HYPOGLYCEMIA IN A PATIENT WITH INSULIN - DEPENDENT DIABETES AND MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Drs. Shireen Chacko and Patamaporn Lekprasert from the Albert Einstein School of Medicine.

Insulin autoimmune syndrome (IAS) and exogenous insulin autoimmune syndrome (EIAS) are characterized by hypoglycemia, hyperinsulinemia and the presence of insulin antibodies (IAs). This case illustrates the diagnostic dilemma that is faced with regard to distinguishing EIAS from IAS in a diabetic patient on insulin with persistent fasting hypoglycemia who interestingly also had monoclonal gammopathy of undetermined significance (MGUS).

We describe an 80-year-old man with coexistent IgG kappa monoclonal gammopathy of undetermined significance (MGUS) and Type 2 Diabetes Mellitus who presented with recurrent episodes of symptomatic fasting hypoglycemia. Elevated plasma insulin (>1000 mcIU/ml), proinsulin (78 pmol/L) and C-peptide (4.5 HI) levels were detected. CT abdomen and endoscopic ultrasound ruled out endogenous insulin over-production from insulinomas. Over several weeks insulin and oral hypoglycemic agents were withdrawn and a low-carbohydrate diet started with frequent small meals and a bedtime snack. Elevated IAs (>625 uU/ml) were detected while he was off insulin for 6 weeks. Anti-IA2, Anti-ZnT8 and Anti GAD-65 were negative. The fasting hypoglycemic episodes resolved eventually when he was off all anti-diabetic medications but post-prandial hyperglycemia persisted for which Linagliptin was added. Bone marrow biopsy ruled out multiple myeloma, therefore the MGUS was not treated.

There are two broad scenarios in which IAs, hypoglycemia and hyperinsulinemia may occur. The first, EIAS, occurs when IAs are produced in response to exogenous insulin administration. The second scenario, IAS, is characterized by IAs without prior exposure to insulin. These two conditions are difficult to definitively distinguish from each other clinically. Whereas EIAS usually resolves with cessation of insulin, IAS may be self-limited or subside after removal of trigger factors, virus or drugs, and rarely requires immunosuppression or plasmapheresis. It is interesting that our patient had MGUS, an association reported previously in IAS. Although he achieved symptomatic relief of hypoglycemia merely with cessation of insulin without treatment of MGUS, the IAs still remained elevated 6 weeks later, and we wondered whether this was due to the underlying monoclonal gammopathy. However, as IAs may persist for up to 2 years after insulin cessation, mere elevation of IAs cannot differentiate between EIAS and IAS related to MGUS. Regardless of this diagnostic dilemma, he had a favorable outcome after cessation of insulin and continued follow up of his MGUS.

SESSION-2: PERSONALIZED PHARMACOTHERAPY FOR PATIENTS WITH T2D

TCF7L2 GENETIC VARIATION AND THE ACUTE GLYCEMIC RESPONSE TO METFORMIN IN PATIENTS WITH TYPE 2 DIABETES

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr Vitaly Baranov, MD, from North-Western State Medical University named after I.I. Mechnikov St. Petersburg, Russia.

TCF7L2 may affect fasting and postprandial hyperglycemia in carriers of the rs7903146 polymorphism due to its crucial role in hepatic glucose production. Metformin functions by reducing hepatic glucose production while simultaneously increasing peripheral glucose uptake. Thus, the intensity of response under application of metformin may depend on the presence of TCF7L2 gene polymorphism. The aim was to analyze the association between rs7903146 polymorphism of the TCF7L2 gene and acute metformin glycemic response in patient with newly diagnosed type 2 diabetes (T2D) measured by continuous glucose monitoring (CGM).

"We genotyped rs7903146 in 77 patients with newly diagnosed T2D. Both gender (39% male) aged 35-72 years, body mass index 33.9±4.3 kg/m2, HbA1c 9.2±1.5 % and treatment naïve to metformin were included. All patients received metformin at an initial dose of 1500 mg per day. Glycemic parameters such as, mean 24-hour glucose level, minimum 24-hour glucose level and 24-hour standard deviation (glycemic variability) were derived from data collected with a CGM system iPro2 after the 5th half-life of drug. Analyses were performed in Statistica for Windows version 10.0 (StatSoft Inc., USA). A p-value of less than 0,05 was considered significant."

The frequencies of the CC, CT and TT genotypes were 57.1%, 36.4% and 6.5% respectively. Minor allele T frequency was 0.25. Genotype distribution followed Hardy-Weinberg equilibrium. All patients receiving 1500 mg of metformin per day, were divided into two groups based on rs7903146 genotype: CC genotype carriers (n=44) and CT/TT genotype carriers (n=33). The mean 24-hour glucose level and the minimum 24-hour glucose level tended to be higher in CT/TT genotype carriers than in CC genotype carriers: 6.2 [5.9; 6.9] versus 6.0 [5.8; 6.2] mmol/l (p=0.23) and 4.2 [3.7; 4.3] versus 3.8 [3.3; 4.4] mmol/l (p=0.31) respectively, but these were not statistically significant. We observed no differences in the measures of glycemic variability between the two groups: 24-hour standard deviation of CC genotype carriers was 0.9 [0.8;1.1] mmol/l versus 0.8 [0.6; 1.0] mmol/l of CT/TT genotype carriers (p >0,05). Additionally, no significant differences in prescribed dose change were observed among the different genotypes after 3 months of observation (x^2=0,12; p=0,94).

There is a considerable variability in the effect of metformin. The glycemic response to metformin is consider has been widely associated with a number of gene polymorphisms. Our findings demonstrate that common variant of TCF7L2 rs7903146 does not influence acute glycemic response to metformin in type 2 diabetic patients. In summary, a more complete investigation of TCF7L2 variants may identify novel polymorphisms which can affect the metformin response.

SEVERE HYPERTRIGLYCERIDEMIA IN A PATIENT WITH TYPE 2 DIABETES AND PREGNANCY

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Drs. Kelly Hill, MD Tharini Gunapalan, MD David Lieb, MD, FACP, FACE, from Eastern Virginia Medical School (EVMS).

Hypertriglyceridemia affects 10% of adults and is associated with obesity and type 2 diabetes. Severe hypertriglyceridemia (> 885 mg/dL) increases the risk for pancreatitis and in pregnancy can be life-threatening to both mother and fetus. We present a patient with severe gestational hypertriglyceridemia and discuss management issues specific to pregnancy.

37-yo woman presented to the ED with nausea, vomiting, and abdominal pain at 19 weeks gestation. PMH was significant for type 2 diabetes, alcohol abuse and recurrent pancreatitis. She denied current alcohol use. Her diet included fried foods and sugar-sweetened beverages. She endorsed difficulty adhering to her lipid and diabetes medications. Her abdomen was tender to palpation and there were no skin rashes. Labs were significant for TGs greater than 3,500 mg/dL, total cholesterol of 815 mg/dL, LDL 36 mg/dL, and HDL < 5 mg/dL. HbA1c was 8.0%. Amylase, lipase, renal function and thyroid tests were normal. As CT imaging was contraindicated an abdominal ultrasound was performed and was unremarkable.

A clinical diagnosis of pancreatitis was made and she was started on IV insulin and fish oil 4 grams daily. TGs decreased to 735 mg/dL prior to discharge. She was provided dietary counseling and was discharged on gemfibrozil, fish oil, and basal insulin, with plan to begin pioglitazone following pregnancy.

Triglycerides rise during pregnancy as the mother adapts to developing fetal needs. This rise becomes clinically significant if the mother has preexisting elevated TGs, as in women with a genetic predisposition, obesity or diabetes. TG-related pancreatitis carries a significant risk of mortality for both mother and child, and its management in pregnancy presents unique challenges. First-line non-pharmacologic interventions, such as weight loss, aerobic exercise, and strict dietary modifications may be difficult or unsafe, and statin therapy is not recommended.

Fibrates reduce triglycerides by >50% and can be given in severe gestational hypertriglyceridemia (after first trimester), though data regarding safety is lacking. Marine omega-3 fatty acids are recommended for reduction in TGs and are considered safe in pregnancy. Optimizing glycemic control is important for reducing TG levels in pregnancy, and insulin activates lipoprotein lipase and reduces TG levels. Though rare, pregnant women who present with pancreatitis may require plasmapheresis.

Given high risk for associated morbidity and mortality, providers should measure TGs in women with a history of hypertriglyceridemia, pancreatitis, or diabetes who are interested in conceiving or who are already pregnant.

SESSION-3: SGLT2 INHIBITORS: HOT TOPICS AND CHALLENGES

PATIENT PERSPECTIVES ON THE USE OF GLP-1RA AND SGLT2 INHIBITORS IN TYPE 1 DIABETES IN CLINICAL PRACTICE

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr. Khary Edwards MD, from University of Texas Southwestern Medical Center.

Use of adjuvant therapies with GLP-1 receptor agonists (GLP-1RA) and SGLT2 inhibitors (SGLT2i) in T1DM is not uncommon. We explored users' perspectives on perceived benefits and side effects with these therapies.

"We conducted a structured telephone interview of adult patients with T1DM who were ever treated with a GLP-1RA or SGLT2i for >3 months at University of Texas Southwestern (Dallas, TX) and Raszeja Hospital (Pozna, Poland). Patients were identified via query of electronic medical records with manual confirmation of T1DM diagnosis. Interview questions were open-ended with responses grouped within predefined categories."

"We interviewed 68 people with T1DM who used GLP-1RA and 82 who used SGLT2i. GLP-1RA users were 73.5% female, 86.8% white, 45±13 years. SGLT2i users were 54.9% female, 90.2% white, 45±13 years. Median (IQR) exposure to GLP-1RA and SGLT-2i was 24.0 (30.5) and 15.7 (24.4) months, respectively; 58.8% and 69.5% were on therapy at time of interview."

Most common reasons reported for treatment initiation were: improved glycemic control

[42/68 (61.8%) vs 67/82 (81.7%) for GLP-1RA and SGLT2i users], weight loss and/or appetite suppression [35/68 (51.4%) vs 19/82 (23.2%)], reduced insulin requirement [9/68 (13.2) vs 9/82 (11%)], and decrease in glucose variability [4/68 (5.9%) vs 17/82 (20.7%)]. Most people (86.8% GLP-1RA and 89.0% SGLT2i users) reported ≥1 benefit attributed to these therapies. Most commonly perceived benefits from the therapy were: improved glycemic control [40/68 (58.8%) vs 68/82 (82.9%), for GLP-1RA and SGLT2i users], weight loss and/or appetite suppression [43/68 (63.2%) vs 25/82 (30.5%)], reduced insulin requirement [19/68 (27.9%) vs 28/82 (34.1%)], and reduced glucose variability [8/68 (11.8%) vs 22/82 (26.8%)]. Side effects perceived to be related to the therapy were more commonly reported by GLP-1RA vs SGLT2i users (63.2% vs 36.6%); 57.4% of GLP-1RA users experienced gastrointestinal side effects while 20.8% of SGLT2i users reported urinary tract and/or mycotic infections. DKA was reported by 4 (4.9%) SGLT2i users and no GLP-1RA user. No episodes of pancreatitis were reported. Of all GLP-1RA users, 14/68 (22.6%) discontinued therapy due to side effects vs 9/82 (11.0%) of SGLT2i users. Of those not currently on product, 60.7% GLP-1RA vs 56.0% SGLT2i prior users were willing to reinitiate the respective therapy.

Most patients with T1DM treated with adjuvant therapy with GLP-1RA or SGLT2i report benefits and are willing to continue such therapy. While GLP-1RA users reported more side effects, many would consider therapy re-initiation. DKA remains a clinical concern in SGLT2i users and they should be closely monitored.

THE EFFICACY AND SAFETY OF A SGLT2 INHIBITORS ON BODY WEIGHT IN OBESE PATIENTS WITHOUT DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Drs. Maria Kezia Pormento, MD, MBASivasthikka Lingarajah, MS Rajni Gautam, MD from Ateneo de Manila University, Manila, Philippines.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been shown to improve glycemic control, lower blood pressure and body weight in patients with type 2 diabetes mellitus (T2DM). Despite obesity being linked to increased risk for numerous diseases, management largely relies on dietary and lifestyle modifications, which are difficult to sustain. The role of SGLT2i to promote weight reduction in non-diabetic patients is a promising venture. This meta-analysis aims to evaluate weight changes in obese, non-diabetic patients who received an SGLT2i.

We employed a systematic search on PubMed, Cochrane, MEDLINE, and Google Scholar databases for relevant articles, using keywords' SGLT2 inhibitors', 'Sodium-glucose co-transporter-2 inhibitors', 'body weight' and 'weight loss,' 'non-diabetic patients.' All original articles published in the English literature on this topic are selected for this study.

Six relevant randomized control trials were included, with a total of 863 patients were identified. The majority were female (79%) mean age of 45.7 ± 11.8 and a body mass index (BMI) of 36.6 ± 5.0. The studies used dapagliflozin, canagliflozin, remogliflozin or sergliflozin with a dosage ranging from 10-300 mg, once to three times a day for 12 to 52 weeks. Our analysis showed a significant weight reduction with the use of SGLT2i in obese non-diabetic patients [weighted mean difference (WMD) -1.56; 95% confidence interval (CI) -2.19, -0.93; I2 = 0%]. Furthermore, BMI and waist circumference were also significantly decreased in the treatment group compared to placebo [WMD -0.5; 95% CI -0.56, -0.44; I2 = 0% and WMD -2.10; 95% CI -3.49, -0.72; I2 = 0%]. Overall, the treatment with SGLT2 inhibitors was generally safe and well-tolerated. The most common adverse event for canagliflozin was mycotic infections (10.3%), pollakiuria (frequent daytime urination) for dapagliflozin (44%), while headache for sergliflozin (33%) and remogliflozin (44%). Urinary tract infection was an adverse event reported in 4/6 studies (7.7% for canagliflozin and 5% for dapagliflozin).

SGLT2 inhibitors are well tolerated and significantly reduce body weight, BMI and waist circumference in obese non-diabetic patients compared to placebo. However, the studies are short-term and vary in specific SGLT2 inhibitor received, dosage and timing. Further studies are required for a definitive conclusion.

CLINICAL AND BIOCHEMICAL OUTCOMES OF SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITORS IN TYPE 2 DIABETES MELLITUS PATIENTS AS A FOURTH ORAL ANTI DIABETIC MEDICINE

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Drs. Muhammad Saleem Nanik Ram Sajjad Ali Khan Zafar Aleem Suchal MD from Aga Khan University Hospital, Karachi, Pakistan.

SGLT-2 inhibitors are a group of oral medications that work independently of insulin working as anti-diabetics by enhancing the excretion of glucose. The purpose of our study was to assess the improvement in terms of HbA1c, weight, blood pressure and BMI and the hepatics and renal effect in terms of SGPT and Creatinine in patients already on three oral glucose lowering agents when SGLT-2 inhibitor was added to their medications.

This retrospective, real world, single center study included 99 patients (mean age [Standard Deviation]: 53.8 [9.63] years) with poorly control type 2 diabetes. Data was recorded at three times, before the addition of SGLT-2 inhibitor and then at 3 and 6 month follow up after the drug had been added in patient's medications. Physical parameters namely weight, BMI and blood pressure were recorded in the clinic while HbA1c, SGPT and Creatinine were checked by laboratory.

Improvement was seen in all parameters at both 3 and 6 month follow up interval. The reduction in HbA1c was statistically significant (P-value < 0.001) with (Mean Reduction [Standard Deviation)) 0.81[1.02] % at 3 months and 1.07[1.11] % at 6 months. Weight was also significantly reduced (P-value < 0.001) with (MR [SD]) 1.83[2.32] kg at 3 and 4.02[6.04] kg at 6 months. Statistically significant reduction (P-value < 0.001) in BMI was also seen with 0.69[0.95] kgm-2 at 3 months and 2.13[3.41] kgm-2 at 6 months of follow up. The systolic blood pressure showed significant reduction (P-value < 0.05) of 5.9[15.76] mmHg at 3 months and 6.37[18.33] mmHg at 6 months. The creatinine and SGPT values of the patient showed minimal variation over the course of these 6 months of follow up.

Our study showed that SGLT-2 inhibitor can be reliably used in patients in which diabetes is not being controlled by other glucose lowering agents and is safe for use in patients in which hepatic and renal function needs to be preserved.

SESSION-4: SUCCESSFUL CO-MANAGEMENT BETWEEN ENDOCRINOLOGY AND PRIMARY CARE – DIABETES

EFFECTS OF VITAMIN D SUPPLEMENTATION ON METABOLIC AND ENDOCRINE ABNORMALITIES IN POLYCYSTIC OVARY SYNDROME

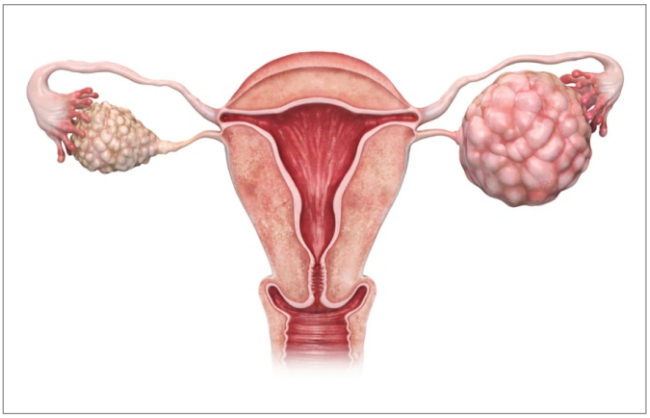
Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr. Javaid Ahmad Bhat, MBBS, MD, DM (Endocrinology) from the Cleveland Clinic Foundation. Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India.

There is growing evidence suggesting the possible role of vitamin D deficiency in the metabolic and endocrine aberrations associated with the PCOS syndrome. In view of these findings this study was proposed to evaluate the vitamin D levels in women with PCOS and to explore the effect of vitamin D supplementation on clinical, hormonal, and metabolic profile of vitamin D deficient/insufficient PCOS women.

The study involved 41 vitamin D deficient/insufficient subjects aged 18–40 years old, with PCOS diagnosed according to the Rotterdam criteria and randomly allocated into 2 groups to take either Metformin treatment plus 4000 IU vitamin D supplementation daily (Group A, n = 20) or Metformin treatment plus placebo treatment (Group B, n = 21) for 24 weeks.

At the baseline two groups did not differ in their age, BMI, hirsutism score, acne grade and



ovarian volumes. The mean Vitamin D levels at the baseline were comparable in two groups with level of 11.2 ng/ml in group A and 15.5 ng/ml in group B.

After the 24-week intervention, compared to the placebo, group A had significant increase in vitamin D levels as compared to group B (11.2 vs. 36.2 ng/ml, p=0.004). Vitamin D supplementation significantly decreased testosterone levels (56.3 vs 42.3 ng/ml, P=0.03), fasting plasma glucose (102 vs. 80 mg/dl, P=0.05), total cholesterol (172 vs. 158 mg/dl, p=0.012), triglycerides (145 vs. 120 mg/dl, p=0.05), and LDL cholesterol levels (107 vs. 102 mg/dl, P=0.01) in group A compared to baseline. However, in group B no such significant changes were observed. However, a significant decrease in fasting insulin levels (p=0.004), and HOMA-IR (p=0.002) was observed in both groups compared to baseline. MATSUDA INDEX was found to be significantly increased in group A as compared to baseline (p=0.024). Nevertheless, the mean of MATSUDAINDEX did not differ in group B as compared to baseline. BMI, menstrual irregularity, hirsutism score, acne grade and ovarian volume did not differ significantly in both groups as compared to baseline.

In conclusion, there was a significant increase in vitamin D levels in vitamin D supplemented group compared to placebo group. Furthermore, vitamin D supplementation for 24 weeks in vitamin D-deficient women with phenotype B-PCOS reduced insulin resistance and hyperandrogenism, as well improving the lipid metabolism, fasting insulin levels and glucose homeostasis parameters, of patients with PCOS to an extent.

CARDIAC ARRHYTHMIAS ARE ASSOCIATED WITH ADVERSE OUTCOMES IN PATIENTS ADMITTED WITH HYPOGLYCEMIA

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr. Kahtan Fadah, DO, from Texas Tech University Health Sciences Center El Paso, El Paso, Texas, United States.

Hypoglycemia has been linked to increased mortality in outpatient and inpatient settings, however, the underlying mechanism is still unknown. Prior observational studies have reported hypoglycemia-induced arrhythmias from bradyarrhythmias to ventricular fibrillation. We examined the Nationwide Inpatient Sample (NIS) for trends and outcomes with hypoglycemia-induced arrhythmias.

We analyzed data for patients admitted to hospitals in the United States (US) from 2016 to 2018 with a primary diagnosis of hypoglycemia using NIS. Further, we selected patients with Cardiac arrhythmias (CAS) and evaluated baseline characteristics and discharge outcomes.

A total of 17310 patients were admitted with hypoglycemia over 3 years, 2210 had different cardiac arrhythmias including atrial fibrillation/flutter (42.0%), sinus bradycardia (30.8%), sinus tachycardia (22%), ventricular fibrillation (0.87%), atrial/ventricular premature complex (8.02%) with some overlap accounting for the total being slightly over 100%. Hypoglycemia with cardiac arrhythmias was non significantly

associated with female gender, (55.1% versus 44.9%, p= 0.082), and older age (60.7 ± 25.7 years versus 47.5 ± 29.7 years, P < .0001). Mean length of stay was higher in hypoglycemic patients with arrhythmias (4.6 ± 5.4 versus 3.6 ± 4.7, p< .0001), as well as total hospital charges (40716±40284 versus 31923 ± 45835, p < .0001). A total of 95 patients died among the cardiac arrhythmia group (50 atrial fibrillation/flutter, 20 sinus tachycardia, 15 sinus bradycardia, 10 ventricular fibrillation, 5 had atrial/ventricular premature complex). The in-hospital mortality was higher (4.1% versus 1.6%, p=0.01) among patients with cardiac arrhythmias (OR: 1.85, CI: 1.07-3.21, p=0.028 in multivariable analysis after adjusting for potential confounders (age, gender, diabetes, coronary artery disease, hypertension, renal failure, heart failure, and dyslipidemia).

These data suggest that hypoglycemic patients with cardiac arrhythmias have worse clinical in-hospital outcomes including higher mortality and could benefit with more aggressive monitoring and management.

SESSION-5: CLINICAL CONVERSATIONS IN DIABETES TECHNOLOGY - AN AACE GUIDELINES UPDATE, PROVIDED BY AN EDUCATION GRANT FROM ABBOTT, MEDTRONIC, DEXCOM

USE OF A CONTINUOUS GLUCOSE MONITORING SYSTEM IN HIGH RISK HOSPITALIZED NON-CRITICALLY ILL PATIENTS WITH DIABETES AFTER CARDIAC SURGERY AND DURING THEIR TRANSITION OF CARE FROM THE INTENSIVE CARE UNIT DURING COVID-19: A PILOT STUDY

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr Anne T Sweeney MD from St. Elizabeth's Medical Center, Brighton, MA, Milton, Massachusetts, United States.

Continuous glucose monitoring (CGM) has demonstrated benefits in managing inpatient diabetes. We initiated this prospective pilot study to determine the feasibility and accuracy of CGM in high-risk cardiac surgery patients with diabetes after their transition of care from the intensive care unit (ICU).

Clarke Error Grid (CEG) analysis was used to compare CGM and point-of-care (POC) measurements. Mean absolute relative difference (MARD) of the paired measurements was calculated to assess the accuracy of the CGM for glucose measurements during the first 24 hours on CGM, the remainder of time on the CGM as well as for different chronic kidney disease (CKD) strata.

Overall, MARD between POC and CGM measurements was 14.80%. MARD for patients without CKD IV and V with eGFR < 20 ml/min/1.73m2 was 12.13%. Overall, 97% of the CGM values were within the no-risk zone of the CEG analysis. For the first 24 hours, a sensitivity analysis of the overall MARD for all subjects and for those with eGFR > 20 ml/min/1.73m2 was 15.42% (+/- 14.44) and 12.80% (+/- 7.85) respectively. Beyond the first 24 hours, overall, MARD for all subjects and for those with eGFR > 20 ml/min/1.73m2 was 14.54% (+/- 13.21) and 11.86% (+/-7.64) respectively.

CGM has great promise to optimize inpatient diabetes management in the noncritical care setting and after the transition of care from the ICU with high clinical reliability, accuracy, and

superior detection of hypoglycemia. More studies are needed to further assess CGM in patients with advanced CKD.

THE ROLE OF PROFESSIONAL CONTINUOUS GLUCOSE MONITORING IN TYPE 2 DIABETICS NOT ON INSULIN

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Drs. Jonas Leibowitz and Dainella Herman from the Lincoln Medical Centre.

There is little data to support the use of professional continuous glucose monitoring (CGM) to improve glucose control in type 2 Diabetics, not on insulin. Professional CGM is able to provide information about glucose patterns, glucose control and hypoglycemia. This study looked for an improvement in A1C measurements after use of a professional CGM.

We evaluated patients with Type 2 Diabetes who do not use insulin who wore a professional CGM (IPRO 2-Medtronic) over a 48-month period in a clinical endocrinology practice. Patients who had an A1C on file within 90 days of wearing the CGM and a follow-up A1C 90 to 180 days after wearing the CGM were included in the analysis. There were 97 patients included in the analysis.

On average the baseline A1C was 7.94% which improved to 7.29% after wearing the CGM. We conclude that non-insulin using patients can benefit from targeted medication changes and lifestyle intervention based on the guidance of a professional CGM. This is important as non-insulin receiving patients are less likely to have a home CGM or perform glucose monitoring.

SESSION-6: TRANSGENDER MEDICINE ACROSS THE SPECTRUM

46, XY 5-ALPHA-REDUCTASE DEFICIENCY IN A PHENOTYPIC FEMALE

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr. James Huynh, MD from the Dwight D. Eisenhower Army Medical Center, Hephzibah, Georgia, United States.

5-alpha-reductase deficiency (5aRD) is a rare genetic sex disorder seen in 46, XY individuals inherited as an autosomal recessive mutation of the 5aR type 2 gene (SRD5A2) resulting in dihydrotestosterone deficiency during sexual characteristic development.

A 36-year-old Pakistani phenotypic female with history of pre-diabetes presented with a new onset type II diabetes mellitus, weight gain, and acne. She had unremarkable surgical and family history. She had never been sexually active and denied ever having a normal menstrual cycle, but did describe intermittent spotting. Physical examination showed BP

130/86 mmHg, BMI 29 kg/m2, thin, pale abdominal striae, central obesity, facial acne, mild hirsutism and moon facies. A low-dose dexamethasone suppression test was negative with cortisol suppressing to < 1.0 mcg/dL.

Further biochemical assessment included normal thyroid function tests, prolactin, DHEA-S and negative hCG. Total testosterone level was elevated to 427 ng/dL (normal 10-55 ng/dL). Dihydrotestosterone (DHT) level was 9.0 ng/dL (normal 4-22 ng/dL). Karyotype revealed a 46XY genotype. Patient denied clitoromegaly or virilization, but endorsed primary amenorrhea. MRI (Figure 1) showed an absent uterus, cervix and ovaries with a blind vaginal pouch posterior to the bladder and anterior to the rectum. The patient was referred for genetic testing and found to be homozygous for a pathogenic variant of the SRD5A2 gene, consistent with autosomal recessive 5ARD.

DHT is a main factor in the development of the external male genitalia. Testosterone is important in the development of internal male genitalia and secondary sexual characteristics. 5-alpha-reductase type 2 enzyme catalyzes the reduction of testosterone to DHT during embryogenesis.

Generally, 46, XY patients with 5ARD present at birth with female features and varying degree of hypospadias, normal female genitourinary anatomy or with clitomegaly. 5ARD has been described in 46, XX females; these individuals have an elevated urinary testosterone-to-DHT ratio, normal female phenotype, absent arm and leg hair with a decrease in axillary and pubic hair due to low DHT (references…). They have late menarche but normal menstrual function and fertility. Management for 5ARD may include initial gender assignment, trial of androgen supplementation, or DHT. This case is atypical as this patient presented at age 36.

This was due to her lack of sexual activity and conservative upbringing. Typically, these patients are identified much earlier as they present with amenorrhea and infertility. This unique case highlights the need for medical providers to consider rare sexual development disorders in the differential for obesity, hirsutism, infertility and amenorrhea.

SESSION-7: CARDIOMETABOLIC EFFECTS OF FATTY KIDNEY DISEASE

CARDIOMETABOLIC EFFECTS OF FATTY KIDNEY DISEASE

Saturday, 14th May 2022

This paper was presented on Saturday May 14th at the 30th Annual Meeting of the American Association of Clinical Endocrinologists (AACE) by Dr. Christian W. Mende, MD, Clinical Professor of Medicine UCSD La Jolla, California, United States.

Dr. Mende's talk was focussed on to -

- Recognize what Fatty Kidney Disease is as a distinct clinical entity.
- Identify the concept of ectopic fat as a driver of metabolic disease in many organs
- Prepare for imaging and therapies that will give Fatty Kidney Disease a place alongside Fatty Liver Disease

Fatty kidney disease merits designation as a specific clinical entity similar to fatty liver disease. Greater attention to this may help encourage research into ameliorating the negative consequences of fatty kidney disease and developing new therapies.

Dr. Mendes and colleagues compared FKD (Fatty Kidney Disease) to fatty liver disease, beginning with non-alcoholic fatty liver disease (NAFLD) and progressing to non-alcoholic steatohepatitis (NASH). NAFLD has been recognized as a risk for albuminuria, CKD, and its progression, but a specific type of renal involvement or renal pathology has not been

described as there are no renal biopsy reports in studies of both NAFLD and CKD combined. As delineated, it is the many risk factors that are shared by both diseases that would be the likely cause of their frequent co-existence.

There are no currently established criteria for the radiological diagnosis of FKD. However, the extensive renal sinus fat (RSF) and perirenal fat accumulations that are routinely seen on magnetic resonance imaging (MRI) or computed tomography (CT) are seldom even mentioned in reports, despite being clinically relevant as risk factors for hypertension and CKD. We argue that they deserve to be recognized and documented in radiological reports. This echoes the lack of reporting on liver fat 25 years ago.

Organ-specific ectopic fat deposition has been described most thoroughly for NAFLD and NASH. However, ectopic fat deposits occur in multiple organs, such as skeletal muscle. In the epicardium, ectopic fat deposits located between the pericardium and myocardium may be mediators of risk for coronary artery disease, heart failure, and atrial fibrillation.

In the kidney, ectopic fat deposits produce FKD. Many effects of the individual components of visceral obesity on the kidney have been well described previously but not in a unifying fashion that this paper proposes to accomplish. Focal intracellular lipid vacuoles accumulated in mesangial cells, podocytes, and proximal tubular epithelial cells positive oil-red-o-staining) have been noted in obesity-related glomerulopathy (ORG). Renal biopsies show cholesterol deposits in some causes of CKD.

FKD may be considered a three-part disorder wherein obesity leads to three distinct clinical presentations, each with a different impact on the kidney and on systemic manifestations. We describe FKD in a pathophysiologic manner as a new entity encompassing three distinct elements:

1. The effects of **intraabdominal fat accumulation** on the kidney. This includes hyperfiltration, glomerular hypertension, albuminuria, renal insulin resistance, and release of proinflammatory cytokines.
2. The effects of **perirenal ectopic fat**, especially hilar/RSF with (a) physical compression of vascular and nerve bundle, upregulation of the renin –angiotensin–aldosterone system (RAAS) and sympathetic nervous system and increased tubular sodium reabsorption and (b) local release of cytokines.
3. **Parenchymal ectopic fat** deposits

Autopsy specimen of fatty kidney

Effects of visceral obesity on the kidney overall

The overall milieu caused by visceral obesity must be taken into account as a component of FKD. Obesity itself is associated with increased renal tubular sodium reabsorption followed by initial hyperfiltration and subsequent gradual decline of estimated glomerular filtration rate (eGFR). Adipocytes are able to secret all components of the RAAS and are found to be upregulated in obesity.

Effects of ectopic fat deposits in the perirenal space, the hilum, and the sinus

Deposition of fatty tissue occurs in several areas of the kidney, including the retroperitoneal space, the perinephric space outside the renal capsule, the hilum, and the sinus area. All of these can contribute to direct physical compression of the kidney, interfering with renal function.

In type 2 diabetes the perirenal fat thickness has been shown to be an independent predictor of renal dysfunction, loss of eGFR, increased renal resistance, and hyperuricemia. Ultrasound evaluation of perirenal fat thickness predicted early kidney injury in obesity.

Effects of renal parenchymal fat deposits

Ectopic intrarenal parenchymal lipid deposits cause lipotoxicity with albuminuria and CKD and also have systemic effects. Cellular uptake of lipids from the circulation in the form of FFA, TG, or cholesterol is facilitated by fatty acid transport proteins and other transporters and are stored as tiny lipid droplets (20-40 nm). This occurs in the kidney in multiple cells, including podocytes and proximal tubular epithelium and mesangial cells.

In summary, the numerous effects of intrarenal parenchymal fat deposits create both damage to the kidney and systemic effects contributing to metabolic syndrome.

Recognizing FKD Clinically - The Need for Radiographic Imaging

NASH and NAFLD were not reported on abdominal imaging until their clinical importance was recognized. Since then, imaging characteristics of NASH and NAFLD have helped to develop the understanding of fatty liver disease and have led to important innovations.

FKD is currently in the same situation that NASH and NAFLD were 20 years ago. Radiologic reports of MRI and CT scans of the abdomen typically do not elaborate on the presence of ectopic renal hilar or sinus fat, presumably being unaware of its clinical significance. It would help the understanding and recognition of FKD as a distinct entity if radiologists can help define the imaging criteria for FKD.

Currently, renal cortical fat deposits are difficult to measure except with Proton MRI. There are issues of the boundary of the renal capsule and perirenal fat and the paucity of intrarenal fat normally. Advances in renal ultrasound, CT, and MRI may be able to overcome these obstacles and allow a radiographic diagnosis and better characterization.

MRI and CT are presently able to delineate only perirenal fat, hilar fat, and RSF. Hilar fat and RSF should perhaps be considered a combined "entity" because a demarcation is not possible. The assessment of renal triglyceride content by Dutch groups is encouraging.

Noninvasive molecular imaging of kidney disease is progressing and, it is hoped, can measure renal triglyceride/fat as well.

In a weight loss study, MRI was able to assess fat loss in RSF but could not detect any change in renal parenchymal fat.

Ultrasound elastography of the kidney may be a technique to measure renal fat content. Sonographic evaluation of para- and perirenal fat thickness has been used as a predictor of early kidney damage in obese patients. B-mode renal ultrasound targeting perirenal fat thickness in specific locations is showing promise. "Para and peri-renal fat ultrasonographic thickness may be … a useful tool for the assessment of visceral fat and early kidney damage in obese adults".

Much might be learned from such imaging and some centers are beginning the radiographic exploration of FKD.

Because visceral obesity affects multiple organs, it is plausible that FKD occurs whenever NAFLD occurs, as suggested by human and animal studies.

If this is confirmed by imaging studies, it may be possible to infer the presence of FKD whenever NASH is identified, thus obviating the need for specific renal imaging. To the extent that imaging can quantify the degree and location of ectopic fat, there may a quantifiable threshold of visceral obesity that initiates the pathological consequences in the kidney as it appears to do in the liver.

Similarly, there may be implications for recognizing that the location and amount of fat accumulation in other organs, such as the epicardium, determines the extent of pathological consequences, both systemically and to the organ itself.

Pig data show a 100% correlation between the presence of NAFLD and fatty kidney by renal biopsies and triglyceride measured by MRI 7-Tesla. We postulate that this coexistence also is present in humans, mainly because of many parallel associated factors (metabolic syndrome, insulin resistance, dyslipidemia, proinflammatory state, etc.). No specific type of renal disease has been described when NAFLD and CKD are both present as there are no data published on renal biopsies in that setting. No causal link between NAFLD and CKD has been established, but the relationship has been reviewed in detail.

It is certainly possible that the time course and nature of progression of NAFLD to NASH differs from that of FKD to CKD, but they both would be expected to reflect the toxicity of ectopic fat deposits.

FKD (i.e., all three stated components: ORG, hilar/renal sinus fat, and intrarenal ectopic fat deposits) has been shown to be a major risk factor for CKD initiation and progression for CKD and hypertension in multiple publications.

One key feature of renal cortical lipid deposition (triglyceride and lipid droplets) is podocyte toxicity with albuminuria and CKD development.

The Importance of Fatty Kidney Disease

In and of itself, the concept of FKD, consisting of three distinct clinical components, helps us understand the role of the kidney in contributing to the pathophysiology of diabetes and the cardiorenal consequences.

It also advances the unifying concept of visceral obesity as a multiorgan systemic disease that has many opportunities for prevention and treatment. FKD recognizes that the kidney is not just a victim but rather an active co-conspirator in diabetes and metabolic syndrome.

AACE
ANNUAL MEETING
May 12-14, 2022

sanofi

MAT-IN-2201259-1.0-05/2022