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Presents

ENDO 2022 - ANNUAL CONFERENCE

ANNUAL MEETING 2022

CONFERENCE COVERAGE NEWSLETTER

TOP 10 SESSIONS

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Novel Technologies and Experimental Platforms for the Study of Human Diabetes Pathophysiology - Organ-On-A-Chip Solutions for Diabetes Research

Novel Technologies and Experimental Platforms for the Study of Human Diabetes Pathophysiology

Sarah Stanley, MB Bchir, PhD

The focus was on new and emerging appro-aches in bioengineering and single cell analyses to study human cell and tissues. The investigator's topic covered using cutting-edge technology in their work and discuss the implementation of new approaches and technologies. Some excerpts from her talk are highlighted below.

For most of human history food supply has actually been pretty unpredictable although there are periods when food is abundant there are also long periods where it's scarce or even absent yet despite this blood glucose is maintained within a pretty narrow range between 70 and 140 milligrams per deciliter and one reason why this is important is because glucose is virtually the sole fuel for the brain or the brain.

Although the brain only weighs 10 percent of body weight it consumes between 16-70 percent of whole-body glucose in the resting state and actually the system for providing glucose to neurons is really highly evolved and beautifully designed so glucose in the circulation is taken up into the extracellular space around neurons through a very high affinity glucose transporter group.

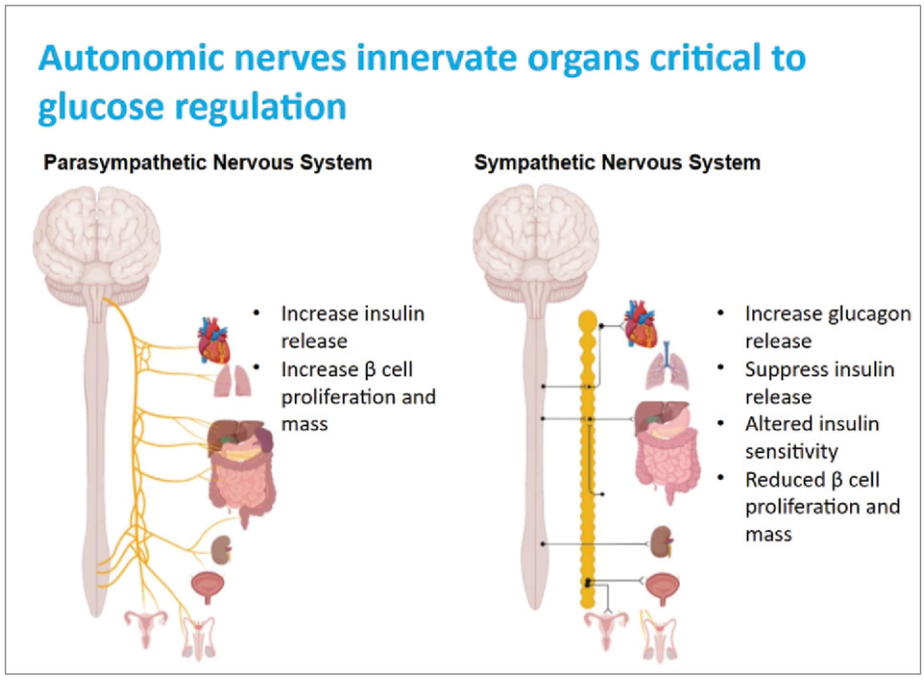
One glucose then goes into the neuron itself through an even higher affinity transporter GLUT3 and there it's trapped within the neuron by phosphorylation to glucose 6-phosphate using hexakinase one.

This system means that under most circumstances neurons can maintain their supply of glucose however they do rely on maintaining blood levels of glucose and if blood levels are very high for a long period of time this leads to high extracellular glucose in central nervous system and can have quite severe osmotic effects which eventually lead to loss of consciousness and even death conversely hypoglycemia in the circulation rapidly leads to a loss of fuel for central nervous system and is again very dangerous leading to loss of consciousness and even death.

There are multiple systems that have evolved to try and maintain blood glucose within a narrow range and we know that some of these systems involve the central nervous system and peripheral nervous system so in order to do so there need to be mechanisms whereby the brain can sense blood glucose and also have effects on peripheral organs to return it to normal. We know that there are specialized neurons that use glucose not only as a fuel but also as a signal and these neurons are actually pretty similar to the endocrine cells within the pancreas some of them are beta-cell-like in that they're activated when glucose levels are high these are called glucose excited neurons others are more like alpha cells and these are switched on when glucose levels are low and our glucose inhibited neurons and when we look at the location of the glucose sensing neurons we can see that they're actually distributed through the central nervous system to form a network.

There have been many studies over the last 50 to 60 years which have looked at the role of the autonomic nervous system in glucose regulation.

These studies include nerve transfection studies electrical stimulation of nerves the use of agonists and antagonists and to summarize these the parasympathetic nervous system which is generally active in the fed state increases insulin conversely the sympathetic nervous system which is generally active during the fasting state or even hypoglycemia acts to increase GLUT1 and suppress insulin and also regulates insulin sensitivity and glucose output from the liver.



Most of these studies have been performed in animal models but there's also a significant amount of evidence to show that neural regulation is important in humans as well and this comes from bread pathologies and also from clinical studies.

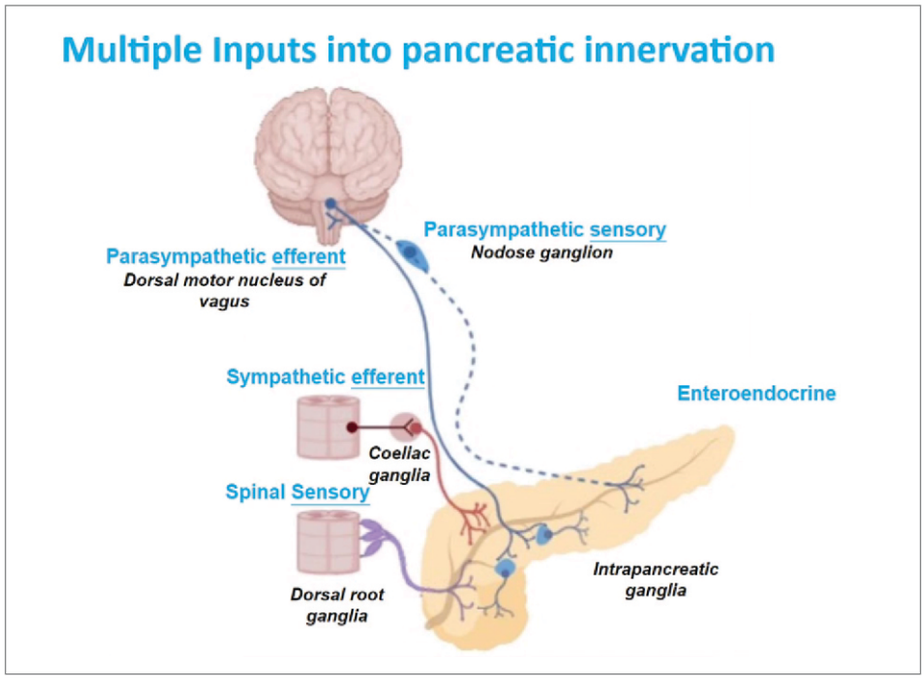
For example, individuals who have hypo-thermic pathology such as space occupying lesions or inflammation have high insulin levels and insulin resistance and may even have impaired glucose tolerance, we also know that there are abnormalities in individuals who have demyelination and finally in individuals who have autonomic neuropathy there are evidence of impaired hypoglycemic responses particularly in the production of glucagon.

There's been many clinical studies in humans as well which has shown following important outcomes –

- Functional MRI studies have shown that there is regional central nervous system activation with hypoglycemia suggesting that there are mechanisms by which human brain can sense changes in blood glucose
- There's also pretty strong evidence for the cephalic phase insulin release so this is a reflex when food is placed in the mouth and before blood glucose is actually changed a neural arc triggers the release of insulin to prepare the body for the coming food
- Studies also have shown that if you also use deep brain stimulation or transcranial magnetic stimulation in individuals who have Parkinson's disease or diabetes or depression respectively and have shown that glucose metabolism is altered in particular a change in hepatic glucose production
- There have been several studies that have looked at the effects of vagotomy in individuals and they're kept on glucose tolerance and although these are not conclusive there are at least some which suggests that glucose tolerance is abnormal in individuals with leucotomy
- And finally, we also know that in individuals who have pancreatic transplants and before there's re-innovation there's an abnormal response to exercise and hypoglycemia

These studies suggest is that neuroregulation of glucose is important in animals and in humans and it's possible that we might be able to harness these neural signals to control blood glucose but in order to do so we need to have a better understanding of the anatomy and function.

The parasympathetic inputs into the pancreas arise from the dorsal motor nucleus of the vagus in the brain stem and androgen study tracing studies



from this region has shown that they provide inputs into the intrapancreatic ganglia.

There have also been some functional studies which show that if you activate the dorsal motor nucleus of the vagus then you can see CFOs which is a marker of neuronal activation and about 10 to 30 percent of the intrapancreatic ganglia another input into the pancreas is actually from the sympathetic nervous system.

Here the pre-ganglionic neurons are in the intermedia lateral column of the spinal cord and project the celiac ganglia in the abdomen via the splanchnic nerves the sympathetic postganglionic fibers then project from the celiac ganglia to the pancreas and have been shown to innovate the intrapancreatic ganglia the eyelids the vasculature and also lymph nodes veining around the pancreas this extensive sensory innervation of the pancreas.

Some of the sensory innervation is bagel and this involves both the exocrine and endocrine pancreas and work from the chicedo group has shown that these neurons are primarily chemosensors.

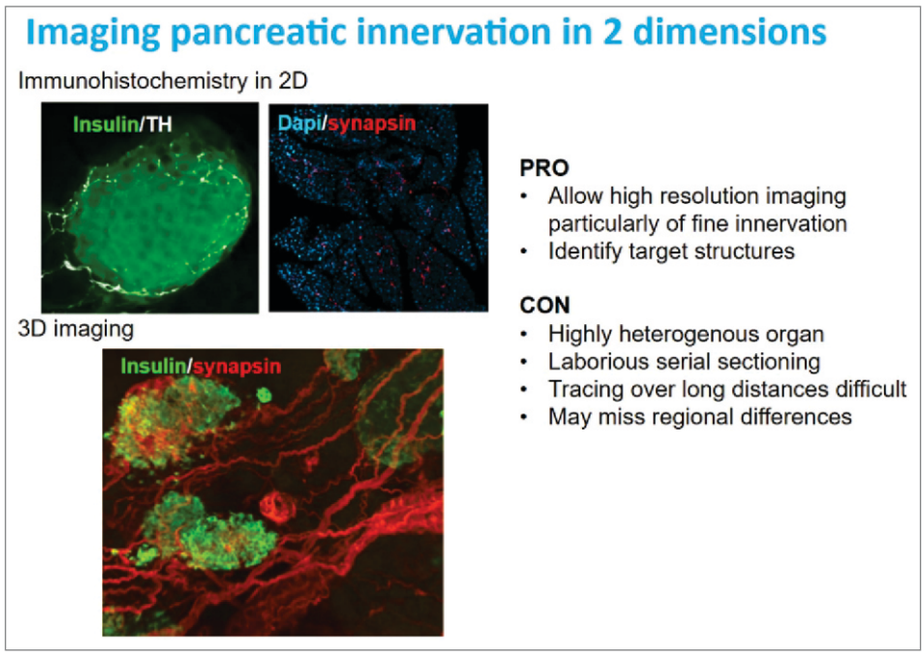
We know that there's also extensive spinal sensory innervation involving T5 through T13 and these spinal sensory nerves express substance P, TRPV1 and CGRP and it's likely that these sensory neurons from the spinal cord are both mechano and chemo sensors in addition to these there's also an extensive network of neurons and intra pancreatic ganglia that form a mesh within the pancreas the intrapancreatic ganglia are often adjacent to the islets.

Studies from Tang et al., have shown that these form neural insular complexes both the ganglia and the fibers from the ganglia are primarily cholinergic but they also express neuropeptides such as vaso-intact vasoactive intestinal peptide. There's been really extensive examination of pancreatic innovation in two dimensions

Studies which have shown both the connections between the nerves and also between individual endocrine cells within the islets themselves.

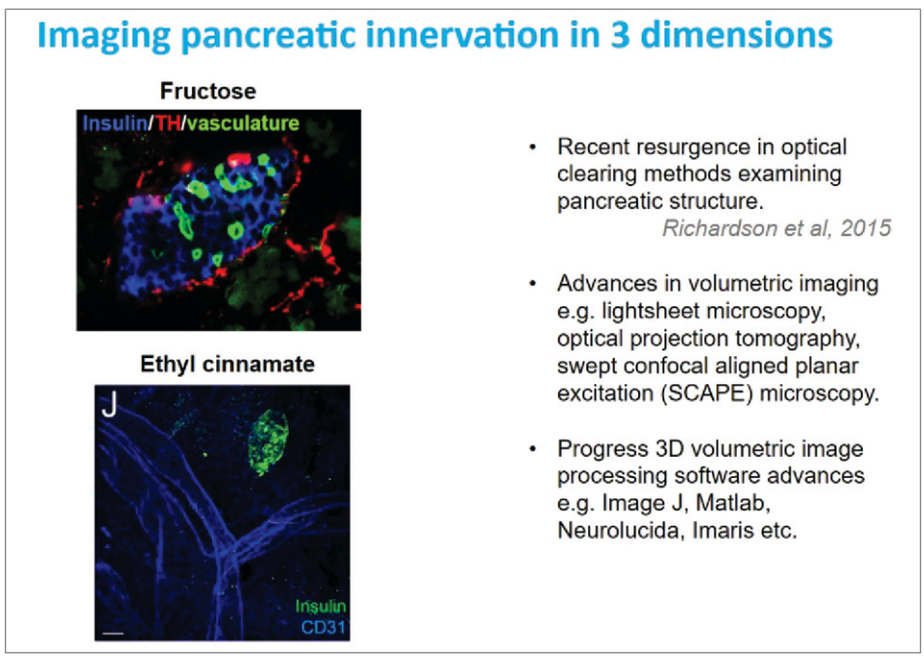
Studies have shown is there's actually extensive parasympathetic and sympathetic innovation in rodent highlights but if you look at human eyelets then the innovation seems to be much more sparse and rather than being parasympathetic it seems to be primarily sympathetic.

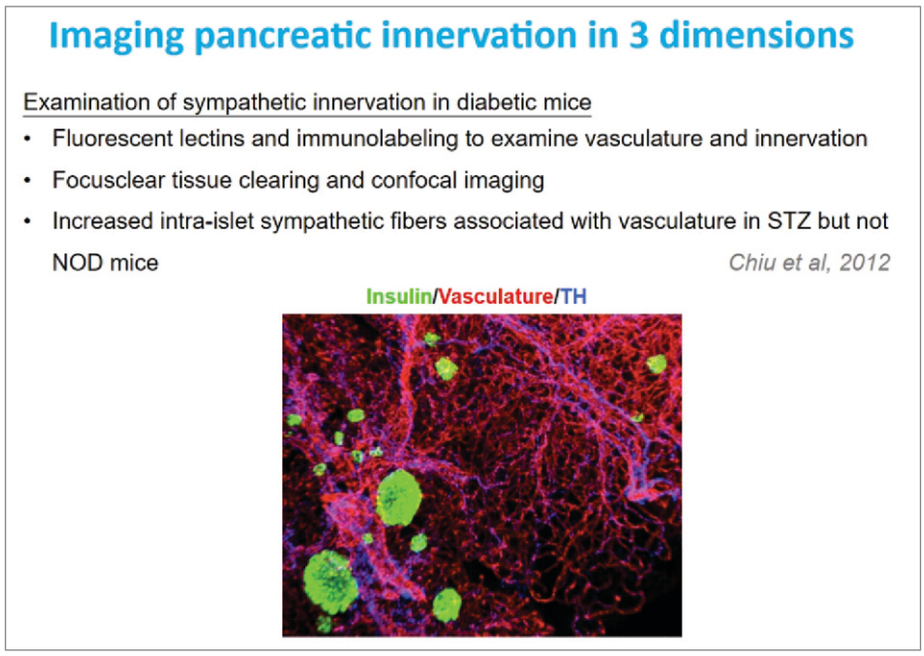
The advantages of two-dimensional imaging are that it allows really high-resolution imaging particularly of the fine structure of the innovation within the eyelets and as mentioned previously you can identify the nerve fibers and how they are adjacent to individual endocrine cells.



However, the downside of the two-dimensional imaging is that the pancreas itself is very heterogeneous and in order to process a whole pancreas particularly human pancreas this requires very laborious cereal. The other disadvantage is that if you're looking at filamentous structures particularly nerves or vasculature then tracing them over long distances can be quite difficult and because you're taking snapshots through the pancreas you may miss regional differences across the whole pancreas.

There's been a resurgence in optical clearing methods to examine pancreatic structure. A snapshot of some of the images that was obtained with these alongside the resurgence in optical clearing methods are shown. There's also been advances in volumetric imaging particularly like sheet microscopy optical projection tomography and scape microscopy and the third component has also been the progress that's been made in the software for 3D volumetric processing these include open source but also commercial software such as Nuerolucida and Imaris.





There's been quite a lot of work done recently looking at pancreatic innovation in three dimensions.

A study from Chiu et al., which examined sympathetic innovation in diabetic mice. Here they use fluorescent lectins and immunolabel to examine vasculature and innervation and a commercial tissue clearing focus clear followed by confocal imaging.

We can see in their paper that they show that there's intra eyelet synthetic fibers which are particularly associated with the vasculature and that this is increased in STZ mice model of diabetes but not in non-obese diabetic mice and the illustration here is work that we've done to show that the sympathetic fibers do indeed follow vasculature in the pancreas.

They've also been studies looking at innovation in intrapancreatic area in a genetic model of diabetes mice again using immunolabel to look at innovation and eyelets and a commercial solution rapidly followed by tiled confocal imaging and one study illustrated the structure of the intrapancreatic ganglia and also that as these ganglia increase in size then their connections to surrounding islets increase in number and they also demonstrated that pancreatic synthetic innovation is increased in the db/db mice.

More recently there have been several papers that have looked at human pancreatic tissue so from Tang et al., was an examination of the sympathetic and parasympathetic innovation in human pancreas and in the contrast to the 2D imaging they suggest that there is some sympathetic innovation of the vascular of the vasculature and also the islet core itself and they also demonstrate a parasympathetic innervation of the islet core.

A recent study looked at sensory innovation of human islets and intrapancreatic ganglia and showed that the sensory fibers go to the ganglia themselves but not the islets in human tissue and finally work from Ralph Campbell Thompson's group has shown that the sympathetic innervation of violence and that this is actually reduced in auto antibody positive individuals compared to either controls or those with type 1 diabetes.

Rescuing Alpha Cell Responses to Hypoglycemia in Type 1 Diabetes

This paper was presented as a part of the session "Novel Technologies and Experimental Platforms for the Study of Human Diabetes Pathophysiology - Organ-On-A-Chip Solutions for Diabetes Research" by Dr. Julia Panzer.

Insulin is a hormone produced by only one cell type in our body, the beta cell. Insulin is important for cells to be able to take up glucose, the main energy source of the body. However, in type 1 diabetes (T1D) the beta cells are destroyed, so no insulin is being produced. Consequently, glucose cannot enter the cells and accumulates in the blood. Patients with T1D need to inject insulin to lower blood glucose levels.

But insulin administration is challenging. If too much insulin is injected, blood glucose levels can drop dangerously low. The first and most important defense against this drop is glucagon secretion from alpha cells, the beta cells' neighbors. Glucagon opposes the effects of insulin by activating the production and release of glucose into the blood stream.

Alpha and beta cells are neighbors for a reason: they communicate. Signals between the two cell types tell them when to start and stop working. If the beta cell secretes insulin, the alpha cell is silent and the other way around. If the beta cell is destroyed in T1D, the alpha cell is left without the beta cell signals and starts working around the clock rising blood glucose levels even more.

However, when blood glucose levels drop and alpha cell action is needed, they are too exhausted to respond appropriately. Our aim is to reactivate these signals and test if that can rescue the alpha cell's ability to respond to low glucose levels in T1D, allowing more effective diabetes therapy.

Mineralocorticoid Receptors Mediate Diet-Induced Lipid Infiltration of Skeletal Muscle and Insulin Resistance

This paper was presented as a part of the session "Novel Technologies and Experimental Platforms for the Study of Human Diabetes Pathophysiology - Organ-On-A-Chip Solutions for Diabetes Research" by Prof. Guanghong Jia, PhD Assistant Research Professor from the University of Missouri School of Medicine.

Consumption of a Western Diet (WD) has been shown to activate mineralocorticoid receptors (MRs) to promote metabolic syndrome. However, our understanding of the precise mechanisms by which enhanced MR activation promotes skeletal muscle insulin resistance remains unclear. Six-week-old C57BL6J mice were fed either a mouse chow diet or WD with or without spironolactone (1 mg/kg/day) for 16 weeks. Spironolactone attenuated 16 weeks of WD - induced in vivo glucose intolerance and improved soleus insulin metabolic signaling (protein kinase B and AMP kinase α pathways). Improved insulin sensitivity was accompanied by increased Glut-4 expression in conjunction with decreased intramyocellular lipid content and reduced free fatty acid (FFA) levels and CD36 expression in soleus skeletal muscle tissue. Related to this, miR-99a was identified to negatively target CD36 (www.targetscan.org/vert_72/) and elevated CD36 induced excessive FFA uptake, ectopic lipid accumulation, as well as systemic and tissue insulin resistance.

Furthermore, in skeletal muscle cells spironolactone prevented enhanced MR signaling mediated reduction of miR-99a and related increased CD36. These data indicate that inhibition of MR activation with spironolactone reversed diet-induced reduction of miR-99a, thereby reducing CD36 expression, leading to reduced intramyocellular lipid content and improved soleus insulin sensitivity.

The Relationship of Lipoprotein Fractions as Assessed by Ion Mobility and Insulin Resistance as Measured by the Insulin Suppression Test

This paper was presented as a part of the session "Novel Technologies and Experimental Platforms for the Study of Human Diabetes Pathophysiology - Organ-On-A-Chip Solutions for Diabetes Research" by Dr. Fahim Abbasi, MD et al., from Stanford University.

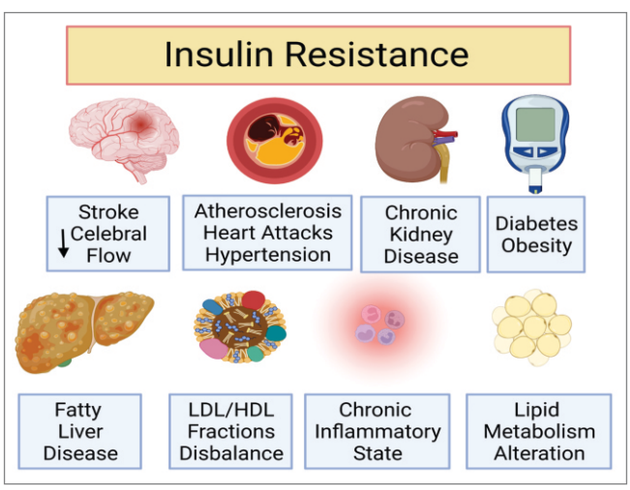
Insulin resistance (IR)/compensatory hyperinsulinemia exert effects on the type and nature of blood lipids that contribute to the increased risk of atherosclerotic cardiovascular disease (ASCVD). Direct measurement of IR is labor-intensive and cannot be performed in a clinical setting.

Previously, we modeled the utility of fasting insulin and C-peptide measurements (IR score) to inform the degree of insulin resistance in a large cohort of individuals without diabetes who had undergone direct measurement of whole-body IR. In the current study, we examined the associations of lipoprotein subfractions with IR and determined the usefulness of lipoprotein subfractions to identify insulin resistant individuals.

A total of 527 persons (median age 50 years, 65% women, 93% non-Hispanic, and 70% white) underwent measurements of BMI, lipid panel, and lipoprotein subfractions by ion mobility (IM) as well as direct measurement of IR by steady-state plasma glucose (SSPG) concentration during the insulin suppression test. Individuals in the top tertile of SSPG concentration were defined as being insulin resistant. A stepwise linear regression model was used to select a combination of lipoprotein subfractions that remained associated with SSPG after adjusting for BMI, age, sex, ethnicity, race, and triglyceride to HDL cholesterol ratio (TG/HDL-C). An IM score was calculated using linear combinations of the regression coefficients for IM lipoprotein subfractions.

Similarly, scores were calculated for TG/HDL-C, the full model excluding the IM lipoprotein subfractions, and the full model that included all variables. The scores were evaluated for predicting the top tertile of SSPG by using area under the receiver operator characteristic curve (AUC) analysis and the positive predictive value (PPV) calculations where the highest 5% value of a score was considered a positive test. Several of the IM lipoprotein sub-fractions were associated with SSPG in a linear regression model after adjusting for BMI, age, sex, ethnicity, race, and TG/HDL-C. When predicting individuals in the top tertile of SSPG, the IM score and TG/HDL-C were similar (AUC=0.68 and 0.70 respectively; PPV=0.59 and 0.59 respectively); however, when used together, they significantly improved the prediction of IR (AUC=0.73; PPV=0.70). Similarly, the score derived from the full stepwise model that included the IM score significantly improved the AUC and PPV when compared with the score from the model that excluded the IM score (AUC=0.84 vs. 0.81; PPV=0.89 vs 0.85).

In **conclusion**, the IM score and TG/HDL-C are comparable in identifying insulin resistant individuals and their combination improves prediction of IR when combined with BMI and demographic data. Among patients who have undergone ion mobility testing, the IM score may assist prioritization of subjects for further testing by the IR score and aid in identification of persons at increased risk of ASCVD associated with IR.



Efficacy and Safety of Avexitide for Treatment of Hypoglycemia After Gastrointestinal Surgery: Assessment of Novel Dosing Regimens in An Expanded Indication

Post-bariatric hypoglycemia (PBH) is a rare disease characterized by recurrent episodes of severe, symptomatic hyperinsulinemic hypoglycemia (HH). The predominant form occurs after Roux-en-Y gastric bypass (RYGB). However, severe cases also present after other upper-gastrointestinal procedures.

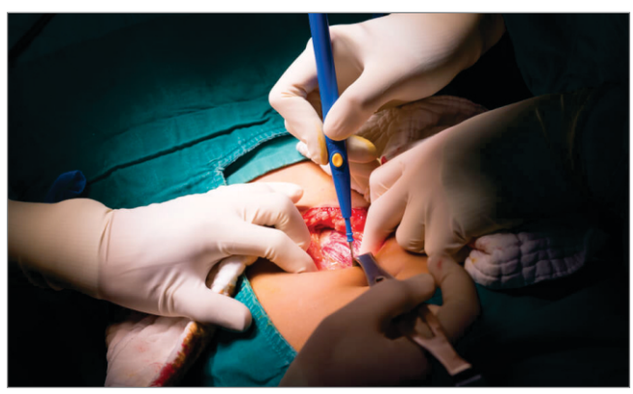
The mechanisms mediating PBH have long been debated, though a critical role for excessive postprandial secretion of glucagon-like peptide-1 (GLP-1) has been established. Avexitide (exendin 9-39) is a first-in-class GLP-1 receptor antagonist in development for treatment of PBH. Prior studies with avexitide administration have shown normalization of postprandial insulin concentrations and reductions in the occurrence of symptomatic hypoglycemia.

In the Phase 2 multicenter PREVENT trial, avexitide administered to post-RYGB patients at a total daily dose of 60 mg [30 mg twice daily (BID) or 60 mg once daily (QD)] for 28 days was well-tolerated and demonstrated significant reductions in the rates of hypoglycemia, symptoms, and percent time in hypoglycemia. Based on the favorable safety and tolerability profile and dose-response relationship observed, we sought to evaluate whether higher doses of avexitide may further enhance the pharmacodynamic response.

In addition, we sought to extend the evaluation to patients with HH after vertical sleeve gastrectomy, esophagectomy, gastrectomy or Nissen fundoplication. In this Phase 2b, open label, cross over study (NCT04652479), eligible patients included males and females (>18 years of age; BMI ≤40 kg/m^2) with a history of recurrent hypoglycemia refractory to medical nutrition therapy (MNT) and exhibiting at least two severe hypoglycemia events while adhering to MNT over a 14-day period. Metabolic and symptomatic parameters were assessed by self-monitoring of blood glucose (SMBG), e-Diary, and blinded continuous glucose monitor (CGM) during 14 days of MNT as compared to 14 days of MNT + avexitide administered by subcutaneous injection at a dose of 45 mg BID and 90 mg QD in crossover design and random order, for a total of 28-days of treatment. An interim analysis (mixed-effect model) at ~50% completion was conducted (n=8). The primary and secondary endpoints were met with statistical significance.

Compared with MNT alone, avexitide 45 mg BID and 90 mg QD reduced the rate of Level 1 hypoglycemia (SMBG <70 mg/dL) by 66% (p=0.022) and 74% (p=0.010); Level 2 hypoglycemia (SMBG <54 mg/dL) by 70% (p=0.003) and 93% (p=0.001); and Level 3 hypoglycemia (severe event characterized by altered mental and/or physical function requiring assistance) by 77% (p=0.002) and 93% (p=0.001), respectively. Objective assessment by blinded CGM corroborated SMBG/e-Diary results, demonstrating significant reductions in the rates of hypoglycemia and improvements in percent time in hypoglycemia.

Responses were comparable across surgical subtypes. Greater improvements were consistently observed with once daily (90 mg QD) than twice daily (45 mg BID) dosing and exceeded those reported in the PREVENT trial. Avexitide was well-tolerated, with no serious adverse events. Complete study results will be presented.



« SESSION-2 »

Management of Type 2 Diabetes with CKD

Management of Diabetes and CKD - Empagliflozin Eyed for Outpatient Chronic Hyponatremia

Empagliflozin is a potential treatment for outpatients with chronic hyponatremia due to the syndrome of inappropriate antidiuresis (SIAD), new data suggest.

The sodium-glucose cotransporter 2 (SGLT2) inhibitor Empagliflozin, licensed for the treatment of Type 2 diabetes, raised serum sodium levels and improved neurocognitive function without major adverse effects in a 4-week trial of 14 outpatients with chronic SIAD-induced hyponatremia.

The findings were recently presented at ENDO 2022: The Endocrine Society Annual Meeting, by Sophie Monnerat, MD-PhD candidate in clinical research, Department of Endocrinology, University Hospital Basel, Switzerland.

The Basel group had previously published a paper showing that empagliflozin increased plasma sodium levels in patients hospitalized with SIAD who were also treated with fluid restriction.

In an interview, session moderator Mark E. Molitch, MD, called the new data on empagliflozin "exciting" and said it's enough to merit use. It's likely that all the SGLT2 inhibitors would work. It's well-tolerated...Obviously, they need to do a longer-term study and look at people with more severe hyponatremia, so they need to expand their studies, but it's really promising," he said.

"Based on even these data, we should be able to use it clinically now," said Molitch, professor emeritus of medicine (endocrinology) at Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Hyponatremia: More Than Meets the Eye

Hyponatremia, defined as a serum sodium level below 135 mmol/L, is the most common electrolyte disorder in both the inpatient and outpatient settings. SIAD is one of its main causes, whereby impaired antidiuretic hormone regulation leads to a reduction in free water excretion and water retention in the kidney, with subsequent hypotonic hyponatremia.

There are many causes of SIAD, including central nervous system and pulmonary disorders, cancer, and certain drugs. But it's also often idiopathic and ongoing. In those situations, it's commonly overlooked but shouldn't be, Monnerat said.

"Hyponatremia is a common and clinically relevant issue...Acute hyponatremia is inarguably considered an emergency, whereas chronic hyponatremia is often seen as asymptomatic. However, there's accumulating evidence that these patients have cognitive impairments such as attention deficit, that they are unstable when walking with a propensity to fall, and that they have increased risk for osteoporosis and fractures, and even death, she said.

Indeed, Molitch noted, "With idiopathic inappropriate vasopressin secretion, if there's a distinct cause you always try to fix it, but a lot of people have low sodium levels for unclear reasons. We don't know why, and we pretty much ignore them. We work them up and if the sodium is 128-130 [mmol/L] and they seem to be okay, we haven't really been paying attention."

But he said that several studies have shown that "these people really aren't normal. They have cognitive issues, gait issues, they're unsteady, and if you correct the hyponatremia those things improve."

Current treatments for chronic hyponatremia involve addressing the underlying cause, if possible, along with fluid restriction, but long-term compliance with that is a problem. Oral urea works by increasing free water clearance through osmotic diuresis, but it has a bitter taste that patients dislike, Monnerat observed.

Vasopressin receptor antagonists (vaptans) are very effective, but also very expensive and carry the risk of overly rapid correction.

"So, overall, those treatments are unsatisfactory and we need alternative treatments," she said.

The investigators chose to study empagliflozin. SGLT2 inhibitors work by promoting osmotic diuresis via urinary glucose excretion, with loss of free water.

"We thought that this water clearance was of greatest interest for the treatment of hyponatremia," Monnerat said, noting that this initial effort led to their 2020 publication of 87 patients hospitalized with acute SIAD.

For the new study, they enrolled 14 outpatients with chronic SIAD in a randomized, double-blind, placebo-controlled crossover trial comparing 25 mg/day of empagliflozin versus a daily placebo tablet for 28 days, followed by a washout period and crossover to the other treatment group.

The participants, seven men and seven women, were a mean age of 71.5 years and had a body mass index of 24.4 kg/m^2. Their causes of SIAD were central nervous system disorders in two, chronic pain/stress in one, drug-induced in four, pulmonary disease in three, and idiopathic in four. The average SIAD duration was 45.5 months.

Serum sodium levels remained stable with placebo while increasing from 130 mmol/L to 134 mmol/L with empagliflozin, giving a corresponding treatment effect of 4.1 mmol/L (P = .004). The increase took place during the first week of treatment and plasma sodium levels remained stable through subsequent weeks, Monnerat reported. The Montreal Cognitive Assessment, a very sensitive test for mild cognitive impairment, was used to evaluate neurocognition. At baseline, the patients had a pathological score of 22.7 points, with normal being 26 points or greater. At end of treatment, the empagliflozin-treated group improved by 1.16 points compared to placebo (P = .042), with a particular effect seen in executive function.

However, no differences were seen in quality of life, gait test, or muscle strength. During the question-and-answer period, Molitch commented that these parameters may take longer to resolve following recovery of normal sodium levels, pointing out that "long-term therapy will be important."

There were no serious adverse events and no differences between the treatment groups in terms of thirst, vertigo, headache, or nausea. There were no episodes of hypoglycemia, hypotension, acute kidney injury, or urogenital infection.

The Basel team is now conducting a larger multicenter trial called EMPOWER (Empagliflozin in Patients with Euvolemic and Hypervolemic Hyponatremia). Results are expected early 2023.

Empagliflozin May Decrease Risk of Kidney Stones in People with Diabetes

The diabetes drug empagliflozin may decrease the risk of kidney stones in patients with type 2 diabetes, according to a new study presented at the ENDO 2022.

Diabetes is a well-known risk factor for kidney stones. Empagliflozin (Jardiance) is an SGLT2 inhibitor. This is a newer class of glucose-lowering medications that has been shown to have significant heart and kidney benefits in patients with type 2 diabetes. These benefits were also seen in people with heart failure and chronic kidney disease without diabetes in clinical trials.

Researchers used existing data from 20 randomized clinical trials to evaluate whether empagliflozin reduced the risk of kidney stones. They pooled data from 15,081 type 2 diabetes patients. Of these, 10,177 received empagliflozin and 4,904 received a placebo.

Patients took either empagliflozin or a placebo for about 1 ½ years. "Compared with placebo, treatment with empagliflozin was associated with an approximate 40% reduced risk of kidney stones in type 2 diabetes patients," said lead researcher Priyadarshini Balasubramanian, M.D., of the Yale School of Medicine in New Haven, Conn. "While we do not know the precise mechanism underlying this benefit, the findings mean that empagliflozin may be used to prevent kidney stones in individuals with type 2 diabetes."

"Based on these findings, further research is needed to confirm these initial observations in patients with and without type 2 diabetes," Balasubramanian said.

Addressing Stress and Postpartum Symptoms Early May Reduce Risk for Type 2 Diabetes in Women

Addressing stress early on in postpartum women who recently experienced gestational diabetes might help curb an increased risk for type 2 diabetes, according to research being presented at the ENDO 2022.

"Gestational diabetes mellitus (GDM) has been shown to increase the risk for postpartum depressive symptoms, or the "maternity blues," which can limit women's ability to practice healthy behaviors," said Jennifer Dias, B.A., a medical student at the Icahn School of Medicine at Mount Sinai in New York, N.Y.

Dias, whose clinical research areas of focus include pregnancy complications and gestational diabetes, worked with colleagues to identify key factors associated with depressive symptoms following childbirth among women with recent gestational diabetes (GDM) from the Balance after Baby Intervention study. The two-year study for the prevention of type 2 diabetes in women with GDM was performed at Brigham and Women's Hospital in Boston, Mass., and the University of Colorado Hospital and Denver Health Medical Center in Aurora, Colo. The study included 181 women between 2016 and 2019.

Data reveal 19% of women scored >9 on the Edinburgh Postpartum Depression Scale and 53% of women scored >14 on the Perceived Stress Scale at the postpartum visit. Perceived stress was associated with postpartum depressive symptoms.

"To help address postpartum depressive symptoms, it may be important to provide support to decrease perceived stress," Dias said.

Prevention of Type 2 Diabetes by Testosterone in the T4DM Trial: Analysis of Effect Mediation

In men aged 50+ years at high risk of, or with newly diagnosed type 2 diabetes (T2D) testosterone (T) treatment reduced the risk T2D at 2-years by 40% beyond lifestyle change alone (Wittert et al., Lancet Diabetes and Endocrinol 2021).

Determine whether changes in total fat mass (kg), abdominal fat mass (%), lean mass (kg), and non-dominant handgrip (kg) mediate the effect of T treatment on glycaemia.

The effect of testosterone on glycaemia is mediated by changes in fat and functional skeletal muscle mass.

A randomized placebo-controlled trial enrolled 1007 men, 50-74 years, waist circumference (WC) ≥95 cm, serum total T ≤ 14 nmol/L (chemiluminescent RIA) and either impaired glucose tolerance or newly diagnosed T2D on an oral glucose tolerance test (OGTT). Participants were enrolled in a lifestyle program (WW) and randomized 1:1 to 3 monthly IM injections of 1 gm testosterone undecanoate or placebo. The primary outcome of T2D at 2-yrs (OGTT ≥11.1 mmol/L) was assessed by binomial regression with a log-link function. Mediators of interest were fat mass % abdominal fat, lean mass (dual X-ray absorptiometry) and non-dominant hand-grip strength (handgrip dynamometry). Mediation was determined by including the baseline and change at two years for each of the 4 factors of interest in the model.

Significance: P< 0.05. There was no imputation for missing data. There were complete data for 775 men (77.5%). For the outcome of T2D at 2-yrs, the unadjusted RR for treatment was 0.59 (95% CI: 0.43-0.80), which became 0.66 (95% CI: 0.51-0.87) after adjustment for baseline values of the proposed treatment mediators and OGTT. After inclusion of changes in body composition (total fat mass, abdominal fat percentage, lean mass) and

grip strength, the effect of treatment was attenuated, RR 0.85 (95% CI: 0.61-1.19). The individual effects for changes in fat mass, abdominal fat, lean mass, and grip strength were 0.88 (0.64-1.19), 0.79 (0.59-1.07), 0.52 (0.38-0.71) and 0.64 (0.48-0.86) respectively.

After including change in fat mass, the RR increased and the effect of T was no longer significant indicating the decrease in fat mass mediates the effect of T. This did not however, entirely explain the effect of T to decrease risk for T2D. Although lean mass and hand grip strength increased, neither mediated the effect of testosterone on T2D.

The Association of Aldosterone and Endothelin-1 with Incident Diabetes Among African Americans: The Jackson Heart Study

African Americans (AAs) have the highest prevalence of hypertension among United States racial/ethnic groups. Regulators of blood pressure, such as aldosterone and endothelin-1 (ET-1), increase risk of hypertension. Higher aldosterone levels have been associated with higher insulin resistance and increased risk of diabetes. Similarly, ET-1 is known to cause insulin resistance by reducing glucose uptake. However, it is poorly understood how aldosterone and ET-1, which primarily regulate the blood pressure, together are involved in diabetes pathophysiology among AAs. Aim: To examine the individual and combined longitudinal associations of aldosterone and ET-1 with incident diabetes among AAs in the Jackson Heart Study (JHS).

Among 3,914 AA participants without prevalent diabetes in the JHS, linear regression models were used to examine cross-sectional associations of exposures (aldosterone, endothelin-1, and a combined aldosterone-endothelin-1 score [2-8]) with glycemic measures (fasting plasma glucose [FPG], HbA1c, HOMA-IR, and HOMA-β). Longitudinal associations of exposures with incident diabetes were examined using Cox proportional hazard models. Models were adjusted for age, sex, education, occupation, systolic blood pressure, smoking, physical activity, dietary intake, alcohol use and adiponectin.

Aldosterone and the combined aldosterone-endothelin score were positively associated with FPG, HOMA-IR, and HOMA-β. Endothelin-1 was negatively associated with FPG but positively associated with HOMA-β. Only the aldosterone-endothelin score was positively associated with HbA1c. A 1-SD higher serum aldosterone and endothelin-1 were associated with a 22% and 14% higher risk of incident diabetes, respectively, while a 1-point higher aldosterone-endothelin score was associated with a 13% higher risk of incident diabetes after adjustment for diabetes risk factors.

The study indicates both aldosterone and ET-1 are risk factors for the development of diabetes among AAs, thus future studies should consider aldosterone and ET-1 modulation to improve glucose metabolism.

Ethnic Differences in Albuminuria Among Adults with Diabetes and Normal Range Estimated Glomerular Filtration Rate (eGFR)

Diabetic kidney disease (DKD) develops in approximately 40% of adults with diabetes and is the leading cause of chronic kidney disease (CKD). Less is known about early DKD, particularly in ethnically diverse populations that include Black, Hispanic/Latinx, and Asian Americans. Current guidelines recommend that patients with diabetes be screened annually for DKD. Albuminuria is the first sign of CKD and is associated with CKD progression, cardiovascular events, and death. This study characterizes ethnic differences in the prevalence of albuminuria in a diverse population of adults with diabetes with normal range eGFR.

This retrospective study was conducted in a large healthcare system where patients with diabetes are annually monitored for DKD. We identified adults with diabetes aged 45-74 years, eGFR ≥60 mL/min/m^2 based on serum creatinine (using the CKD-EPI equation without race), and assessment of urine albumin-creatinine ratio (ACR), urine protein-creatinine ratio (PCR) and/or urine protein dipstick in 2015. Albuminuria was based on urine ACR (95%), otherwise, from urine PCR (1%) converted to ACR, and, if unavailable, from urine protein dipstick (4%) converted to ACR. The cohort was restricted to patients with diabetes onset after health plan enrollment to calculate diabetes duration. Hypertension was identified by clinical diagnosis. Modified Poisson regression with robust variance was used to examine the association of ethnicity and albuminuria, reporting relative risk (RR) with 95% confidence intervals (CI).

Among 79,184 adults with diabetes, eGFR ≥60, and urine albumin/protein assessment (age 60.5 ±7.7 y, 54.0% male), 40.3% were non-Hispanic White, 9.6% Black, 26.3% Asian/Pacific Islander (PI), and 21.0% Hispanic/Latinx race/ethnicity. 69.9% had hypertension. Overall, 81.7%, 13.8%, and 4.6% had urine ACR <30 (normal), 30 to <300 (microalbuminuria), and ≥300 mg/g (macroalbuminuria), respectively, with albuminuria higher in males than females. By race/ethnicity, the prevalence of [micro/macroalbuminuria] was [15.7/5.4%] Asian/PI, [13.8/4.8%] Black, [13.1/4.5%] Hispanic/Latinx, and [12.8/4.1%] non-Hispanic Whites. Among Asian/PIs, prevalence ranged from [19.5/8.4%] Hawaiian/PI and [18.2/7.1%] Filipino to [14.5/3.6%] Chinese and [11.2/3.4%] South Asian. In multivariable analyses, adjusting for age, sex, diabetes duration, and hypertension, Asian/PI (RR 1.3, CI 1.2-1.3) was associated with higher risk of albuminuria compared to non-Hispanic White, but Black (RR 1.0) and Hispanic/Latinx (RR 1.0) were not. Among Asian/PIs, with Chinese as reference, Filipino (RR 1.3, CI 1.2-1.4) and Hawaiian/PI (RR 1.4, CI 1.3-1.6) had higher risk, South Asian had lower risk (RR 0.7, CI 0.7-0.8), and Japanese and Southeast Asian had similar risk of albuminuria.

The risk of albuminuria in adults with diabetes and normal range eGFR was higher in Asian/PI adults. Among Asian/PIs, the risk was higher among Filipino and Hawaiian/PI and lower in South Asian compared to Chinese adults, supporting the importance of disaggregating Asians when examining microvascular outcomes. Future studies should examine ACEI/ARB use and albuminuria progression.

« SESSION-3 »

Disparities in Diabetes and Programs Which Help

Study Finds Disparities in Access to Insulin Pumps Among Youth with Type 1 Diabetes

Over the past 20 years, despite the overall increase in the use of insulin pumps, there have been few improvements in the ethnic, racial and socioeconomic inequities in insulin pump use among youth with type 1 diabetes, according to a new study presented at ENDO 2022.

"We found there is a huge divide in who actually has access to insulin pumps," said lead researcher Estelle Everett, M.D., M.H.S., of the David Geffen School of Medicine at University of California, Los Angeles in in Los Angeles, Calif. "Racial-ethnic minority groups and those of lower socioeconomic status still have unequal access to this very beneficial management tool. This is really concerning because these groups have more challenges managing their diabetes and have higher risk of complications. Changes in the approach to diabetes care and health policies are needed to ensure equal access to this life-changing diabetes device."

Diabetes that is not well controlled can lead to serious complications like blindness, kidney disease, amputation and heart disease. "Diabetes technology such as insulin pumps have revolutionized diabetes management," Everett said.

Insulin pumps are small handheld devices that administer insulin with the press of a button so patients can discreetly administer their insulin without numerous painful injections. New insulin pumps can also connect to continuous glucose monitors and automatically adjust insulin based on a person's current blood glucose values. These devices have been found to improve diabetes control and reduce the distress related to diabetes care.

The researchers used data from the SEARCH for Diabetes in Youth study to evaluate changes in insulin pump use among participants younger than age 20 with type 1 diabetes from 2001 to 2019. They looked at insulin pump use by racial and ethnic groups, health insurance, household income and formal parental education at different time periods during those years.

They found that at all points of time, the highest rates of pump use occurred in white non-Hispanic patients, those with incomes equal to or greater than $75,000, and those with an education greater than a bachelor's degree. Pump use was lowest in Black patients, those with incomes less than $25,000 and those with a high school degree.

While the overall prevalence of insulin pump use increased from 30% in 2001-2005 to 58.3% in 2016-2019, there was no change in the rates by race, income and education over time.

"Inequities in access to diabetes technologies are unacceptable because everyone deserves the opportunity to improve their diabetes health," Everett said. "Studies that evaluate barriers and test interventions to improve technology access are needed to address the persistent inequities in diabetes care."

Cutting-Edge Translational Strategies in Type 1 Diabetes

The overall goal of this study is to develop precision-targeted therapies for type 1 diabetes (T1D) by blocking the presentation of pancreatic antigens to T cells using an innovative translational approach. There is currently no curative therapy for T1D and the only available treatment is insulin replacement, which – although being life-saving – remains problematic and can be associated with often fatal high or low glucose levels. We hypothesize that the presentation of pathogenic pancreatic peptides to T cells within the HLA-DQ8 pocket is a key trigger in T1D, and that blocking the peptide binding to this pocket can be harnessed to treat/prevent the autoimmune response targeting beta cells in T1D.

We propose to block antigen presentation to treat/prevent autoimmunity in T1D using retro-inverso D-amino acid peptides (RIPs). To test our hypothesis, we used the following tools: recombinant human HLA-DQ8, human B cells homozygous for HLA-DQ8, humanized mice expressing human HLA-DQ8, NOD mice, and peripheral blood mononuclear cells (PBMCs) isolated from new onset HLA-DQ8 T1D patients. All of them represent exquisite translational instruments to evaluate in vitro, ex vivo, and in vivo the functional role of our RIPs in preventing beta cell destruction.

We have identified a RIP (RI-CT) that inhibits InsB:9-23 binding to recombinant HLA-DQ8 molecule, as well as its binding to HLA-DQ8 expressed on a human B-cell line. Specifically, RI-CT averted T-cell activation in a mixed lymphocyte reaction containing human DQ8 cells loaded with InsB:9-23 peptide and murine T-cells expressing a human TCR specific for the InsB:9-23–DQ8 complex. These results were also confirmed in humanized transgenic B6-DQ8 mice (KO for murine MHC-II) both ex vivo and in vivo, as shown by decreased production of pro-inflammatory cytokines (including IL-2 and IFN-γ) and reduced lymphocyte proliferation. Moreover, RI-CT prevents autoimmune diabetes in NOD mice as demonstrated by a significant decrease in pancreatic immune cell infiltration in treated mice versus controls. Importantly, at 25 weeks of age 70% of RI-CT treated mice were protected from the development of diabetes, while as expected 80% of control NOD mice had developed the disease. Interestingly, RI-CT injection also altered T-cell subpopulations in NOD mice significantly decreasing CD8 expression and significantly increasing Foxp3 levels in treated mice. Of note, RI-CT significantly inhibits InsB:9-23-mediated lymphocyte activation in peripheral blood mononuclear cells isolated from new onset DQ8-T1D patients.

In **summary**, we discovered a RIP that blocks InsB:9-23 binding to HLA-DQ8 and its presentation to T-cells averting beta cells destruction, and that delays T1D in NOD mice. These data set the stage for using our approach of blocking antigen presentation by RIP as a novel therapeutic approach for autoimmune diseases in general.

« SESSION-4 »

Molecular Aspects of COVID-19 and Diabetes

COVID-19 Pandemic Stress Impacts Ovulation

Disturbances in ovulation that didn't produce any actual changes in the menstrual cycle of women were extremely common during the first year of the COVID-19 pandemic and were linked to emotional stress, according to the findings of an "experiment of nature" that allowed for comparison with women a decade earlier.

Findings from two studies of reproductive-age women, one conducted in 2006-2008 and the other in 2020-2021, were presented by Jerilynn C. Prior, MD, at ENDO 2022: The Endocrine Society Annual Meeting.

The comparison of the two time periods yielded several novel findings. "I was taught in medical school that when women don't eat enough, they lose their period. But what we now understand is there's a graded response to various stressors, acting through the hypothalamus in a common pathway. There is a gradation of disturbances, some of which are subclinical or not obvious," said Prior, professor of endocrinology and metabolism at the University of British Columbia, Vancouver, Canada.

Moreover, women's menstrual cycle lengths didn't differ across the two time periods, despite a dramatic 63% decrement in normal ovulatory function related to increased depression, anxiety, and outside stresses that the women reported in diaries.

"Assuming that regular cycles need normal ovulation is something we should just get out of our minds. It changes our concept about what's normal if we only know about the cycle length," she observed.

It will be critical going forward to see whether the ovulatory disturbances have resolved as the pandemic has shifted "because there's strong evidence that ovulatory disturbances, even with normal cycle length, are related to bone loss and some evidence it's related to early heart attacks, breast and endometrial cancers," Prior said during a press conference.

Asked to comment, session moderator Genevieve Neal-Perry, MD, PhD, told Medscape Medical News: "I think what we can take away is that stress itself is a modifier of the way the brain and the gonads communicate with each other, and that then has an impact on ovulatory function."

Neal-Perry noted that the association of stress and ovulatory disruption has been reported in various ways previously, but "clearly it doesn't affect everyone. What we don't know is who is most susceptible. There have been some studies showing a genetic predisposition and a genetic anomaly that actually makes them more susceptible to the impact of stress on the reproductive system."

But the lack of data on weight change in the study cohorts is a limitation. "To me one of the more important questions was what was going on with weight. Just looking at a static number doesn't tell you whether there were changes. We know that weight gain or weight loss can stress the reproductive axis," noted Neal-Parry of the department of obstetrics and gynecology at the University of North Carolina School of Medicine, Chapel Hill.

"Experiment of Nature" Revealed Invisible Effect of Pandemic Stress

The women in both cohorts of the Menstruation Ovulation Study (MOS) were healthy volunteers aged 19-35 years recruited from the metropolitan Vancouver region. All were menstruating monthly and none were taking hormonal birth control. Recruitment for the second cohort had begun just prior to the March 2020 COVID-19 pandemic lockdown.

Interviewer-administered questionnaires (CaMos) covering demographics, socioeconomic status, and reproductive history, and daily diaries kept by the women (menstrual cycle diary) were identical for both cohorts.

Assessments of ovulation differed for the two studies but were cross-validated. For the earlier time period, ovulation was assessed by a threefold increase in follicular-to-luteal urinary progesterone (PdG). For the pandemic-era study, the validated quantitative basal temperature (QBT) method was used.

There were 301 women in the earlier cohort and 125 during the pandemic. Both were an average age of about 29 years and had a body mass index of about 24.3 kg/m^2 (within the normal range). The pandemic cohort was more racially/ethnically diverse than the earlier one and more in-line with recent census data.

More of the women were nulliparous during pandemic than earlier (92.7% vs 80.4%; P = .002).

The distribution of menstrual cycle lengths didn't differ, with both cohorts averaging about 30 days (P = .893). However, while 90% of the women in the earlier cohort ovulated normally, only 37% did during the pandemic, a highly significant difference (P < .0001).

Thus, during the pandemic, 63% of women had "silent ovulatory disturbances," either with short luteal phases after ovulation or no ovulation, compared with just 10% in the earlier cohort, "which is remarkable, unbelievable actually," Prior remarked.

The difference wasn't explained by any of the demographic information collected either, including socioeconomic status, lifestyle, or reproductive history variables.

And it wasn't because of COVID-19 vaccination, as the vaccine wasn't available when most of the women were recruited, and of the 79 who were recruited during vaccine availability, only two received a COVID-19 vaccine during the study (and both had normal ovulation).

Employment Changes, Caring Responsibilities, and Worry Likely Causes. The information from the diaries was more revealing. Several diary components were far more common during the pandemic, including negative mood (feeling depressed or anxious, sleep problems, and outside stresses), self-worth, interest in sex, energy level, and appetite. All were significantly different between the

two cohorts (P < .001) and between those with and without ovulatory disturbances.

"So menstrual cycle lengths and long cycles didn't differ, but there was a much higher prevalence of silent or subclinical ovulatory disturbances, and these were related to the increased stresses that women recorded in their diaries. This means that the estrogen levels were pretty close to normal but the progesterone levels were remarkably decreased," Prior said.

Interestingly, reported menstrual cramps were also significantly more common during the pandemic and associated with ovulatory disruption.

"That is a new observation because previously we've always thought that you needed to ovulate in order to even have cramps," she commented.

Stem-Cell Based Therapy Shows Promise in Treating High-Risk Type 1 Diabetes

An investigative stem cell-based therapy called PEC-Direct, designed to act as a replacement pancreas, has the potential to provide blood sugar control in patients with high-risk type 1 diabetes, suggests a clinical study presented at the ENDO 2022.

The study found multiple patients using the new treatment had clinically relevant increases in C-peptide, a substance made in the pancreas along with insulin. C-peptide and insulin are released from the pancreas at the same time and in about equal amounts, so measuring C-peptide can show how much insulin the body is making.

"This research represents the first instance in multiple patients of clinically relevant increases in C-peptide, indicative of insulin production, with a stem cell-based therapy delivered in a device," according to Manasi Sinha Jaiman, M.D., M.P.H., Chief Medical Officer of ViaCyte, Inc., in San Diego, Calif., the company that makes PEC-Direct.

Patients with type 1 diabetes eventually lose the ability to produce their own insulin to control blood sugar levels. Patients must frequently check those levels with finger sticks, inject multiple insulin shots or carry around bulky devices. The injection of insulin also carries the risk of accidentally lowering blood sugar to dangerous levels.

The PEC-Direct device is designed to provide a long-term, stable source of insulin to regulate glucose levels. The device comprises a pouch containing stem-cell derived pancreatic cells which mature into insulin-producing cells once implanted into the body to regulate glucose levels. The open device membrane allows blood vessels to grow into the device to contact the cells. To prevent an immune reaction, patients take immunosuppressive drugs.

The treatment is meant for patients with high-risk type 1 diabetes, who may be especially vulnerable to acute complications due to factors such as recurrent severe low blood sugar, or frequent and extreme blood sugar fluctuations that are difficult to control.

The study included 10 adults with type 1 diabetes who had received their diagnosis at least 5 years prior to the start of the study and were not able to tell when their blood sugar went too low (called hypoglycemia unawareness). Initial data from one patient showed clinically relevant levels of stimulated C-peptide and corresponding improvements in blood glucose control within six months after implantation of PEC-Direct. Since then, increased C-peptide levels were seen in multiple patients, along with decreases in HbA1C (a blood test that measures average blood sugar levels over the past three months) by as much as 1.5%, and decreases in the amount of insulin patients needed to administer by as much as 70%.

"The results suggest stem cell-based replacement therapy has the potential to provide blood glucose control and could one day eliminate the need for injecting or dosing insulin externally," Jaiman said. "The study provides further proof-of-concept that continued optimization of PEC-Direct has promise as a functional cure for type 1 diabetes."

Increased Fracture Risk in Patients Using Insulin Compared to Metformin

Patients with type 2 diabetes have an increased risk for fractures, despite their normal-to-high bone mineral density, according to research being presented at the ENDO 2022.

"Patients using insulin or sulfonylurea are at a high risk of fractures compared to metformin-only users, and the risk could be higher in non-obese and well-controlled diabetic patients," said Sung Hye Kong, M.D., of Seoul National University Bundang Hospital in Seongnam, South Korea.

Kong and colleagues acknowledge that anti-diabetic medications have long been suspected for an increased risk for fractures among this patient population. However, after investigating longitudinal comparative studies, they learned that evidence of these effects are limited.

For their study, the researchers included 6,694 patients aged ≥50 years from the common data model (CDM) database between 2008 and 2011, who used the same anti-diabetic medications for over a year.

They analyzed risks of major osteoporotic fractures and hip fractures in each group using the Cox proportional hazards model compared with a metformin group as a reference.

"From real-world data using the common data model, we found that insulin users were at elevated risk of major osteoporotic and hip fracture compared to metformin users, which was attenuated in users with a combination of insulin and metformin," Kong said.

This increased fracture risk among people who used insulin was exaggerated among people who are not obese and those with well-controlled diabetes. These findings suggest a need for routine fracture risk assessments in patients with diabetes.

« SESSION-5 »

Beyond Glycemic Control: Enhancing Glucose Metabolism and Energy Homeostasis Through Dual Agonism of Incretins

Targeting Hyperglucagonemia Reverses Glucagon Resistance

This paper was presented by Dr. Ernesto Bernal-Mizrachi, MD from the University of Miami.

Elevation of glucagon levels and increase in alpha-cell mass are associated with states of hyperglycemia in diabetes. A better understanding of the molecular mechanisms governing glucagon secretion could have major implications in understanding abnormal responses to hypoglycemia in diabetic patients and provide novel avenues for diabetes management.

Stimulation of glucagon secretion in hypoglycemia, or by amino acids, induces hepatic glucose production via cellular mechanisms including suppression of glycogenesis and glycolysis and stimulation of glycogenolysis and gluconeogenesis.

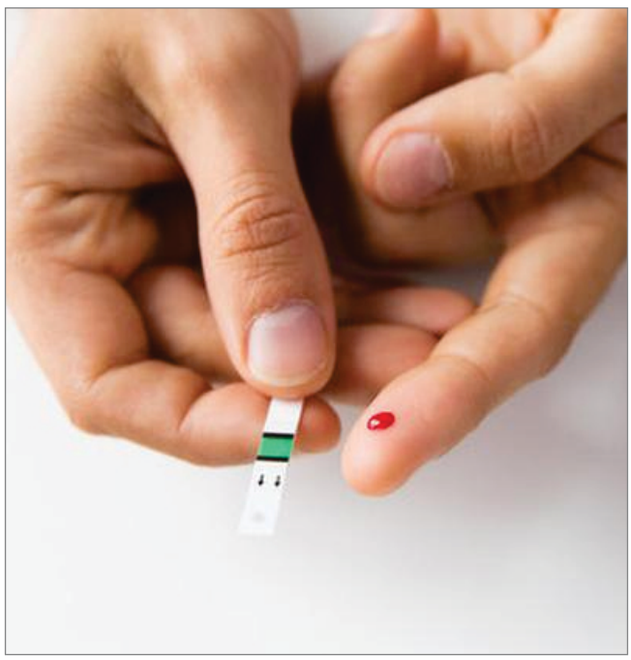
The close link between amino acids and the alpha-cell is highlighted by the liver–alpha-cell axis. This axis was identified by the major increase in alpha-cell hyperplasia and hyperglucagonemia in models of reduced glucagon action in hepatocytes genetically or pharmacologically by treatment with glucagon receptor antagonists, which was subsequently attributed to the dramatic rise in amino acids.

Induction of mTORC1 by constitutive genetic deletion of TSC2 in alpha-cells (aTSC2KO) recapitulated the effects of chronic hyperaminoacidemia with increases in alpha-cell mass and chronic

hyperglucagonemia indicating that mTORC1 mediates amino acids signals in alpha-cells. However, the effects of acute versus chronic induction of alpha-cell mTORC1 signaling on these outcomes have not been explored.

Using mice with doxycycline induction of Rheb (activator of mTORC1 signaling) (aRhebTg) and inducible Cre-mediated deletion of the mTORC1 inhibitor, TSC2, in alpha-cells (iaTSC2KO), we showed that induction of hyperglucagonemia is associated with two phases: Acute phase characterized by impaired glucose tolerance because of increased gluconeogenesis and glucose output by the liver. And a chronic phase, characterized by normalization of glucose tolerance due to downregulation of the hepatic glucagon receptor (Gcgr), Pepck, and some genes involved in amino acid metabolism and urea production. Importantly, the consequences of chronic hyperglucagonemia were reversible after normalization of glucagon levels by turning off alpha-cell Rheb expression.

These studies uncovered the acute versus chronic effects of hyperglucagonemia on glucose homeostasis and further demonstrate that glucagon resistance is a reversible process. These observations provide insight into the impact of glucagon in the pathogenesis of hyperglycemia and the physiological effects of administration of dual GLP1/Glucagon receptor agonists.



« SESSION-6 »

Time in Range - The A1c ?

Achievement of HbA1c <6.5% Without Weight Gain and Hypoglycemia in People with Type 2 Diabetes Treated with Tirzepatide Across the Phase 3 SURPASS Program

This paper was presented by Drs. Alice Cheng, MD from the Unity Health Toronto and University of Toronto and Dr. Pratik Choudhary, MD from the University of Leicester.

Tirzepatide, the novel dual GIP/GLP-1 receptor agonist for the treatment of type 2 diabetes, has been shown to reduce HbA1c and weight, with more patients achieving HbA1c ≤6.5%, compared to placebo and active comparators in the phase 3 SURPASS 1-5 studies. This analysis compared the percentage of patients treated with tirzepatide achieving a composite endpoint of HbA1c <6.5% without weight gain and hypoglycemia in these studies.

"We compared the proportion of participants achieving the composite endpoint between the tirzepatide (5, 10, or 15 mg) and respective comparator groups while patients were on treatment and without rescue medication. Missing data was imputed based on observed data in the same treatment arm from subjects who had their efficacy measure at the endpoint visit assessed after early discontinuation of study drug. End of treatment HbA1c and weight were evaluated at week 40 (SURPASS-1, 2, 5) and week 52 (SURPASS-3, 4). Weight gain was defined as a change from baseline in weight <0.1 kg. Hypoglycemia included blood glucose level <54 mg/dL with symptoms of hypoglycemia or severe hypoglycemia."

In SURPASS-1, 2, 3, 4, and 5 significantly more patients treated with tirzepatide achieved the composite endpoint compared to placebo or comparator (P≤0.002). As a monotherapy in SURPASS-1, significantly more patients treated with tirzepatide 5 mg, 10 mg, 15 mg achieved the composite endpoint than placebo (75%, 78%, 83%, and 5%, respectively; all P<0.001). As add-on to metformin in SURPASS-2, significantly more patients treated with tirzepatide 5 mg, 10 mg, 15 mg achieved the composite endpoint than semaglutide (67%, 77%, 83%, and 59%, respectively; P=0.002, P<0.001, P<0.001, respectively). When compared to basal insulin in SURPASS-3, significantly more patients treated with tirzepatide 5 mg, 10 mg, 15 mg achieved the composite endpoint than insulin degludec (63%, 76%, 82%, and 13%, respectively; all P<0.001). When added to 1-3 oral antihyperglycemics in SURPASS-4, significantly more patients treated with tirzepatide 5 mg, 10 mg, 15 mg achieved the composite endpoint than insulin glargine (56%, 68%, 75%, and 10%, respectively; all P<0.001). As an add-on to basal insulin in SURPASS-5, significantly more patients treated with tirzepatide 5 mg, 10 mg, 15 mg achieved the composite endpoint than placebo (63%, 70%, 76%, and 8% respectively; all P<0.001).

Significantly more patients treated with tirzepatide achieved a composite endpoint of HbA1c <6.5% without weight gain or hypoglycemia than those treated with placebo, semaglutide, insulin degludec, or insulin glargine in the phase 3 SURPASS program.

Bias May Play a Role in Underdiagnoses of Prediabetes

The accurate diagnosis of prediabetes in the primary care setting might depend on a patient's age, BMI, gender, race and certain comorbidities, according to research being presented at ENDO 2022.

Prediabetes is reversible through medications and lifestyle changes, and a correct and timely diagnosis might help prevent stroke and heart disease. The Centers for Disease Control and Prevention (CDC) estimate that 80 to 90% of patients with prediabetes are unaware of their diagnosis, according to An V. Nguyen, MD, a resident with a focus on general endocrinology at Scripps Clinic/Scripps Green Hospital in La Jolla, Calif.

"This study demonstrates that the condition is often appropriately screened, but diagnosis and treatment were less consistent," Nguyen said. "Healthcare providers seem to rely heavily on a Hemoglobin A1c (HbA1c) test, which measures average blood glucose over three months, to make the diagnosis."

Nguyen and colleagues conducted a retrospective chart review of patients who were seen in primary care clinics at Scripps Clinics' five locations in southern California from January 1, 2018, through December 31, 2019. First, the researchers identified all faults who qualified for a prediabetes diagnosis based on fasting blood glucose (FBG) or HbA1c levels. Those with a billable condition were included in the intervention group. The others were part of the control group. They looked at whether factors such as the patients' age, BMI, gender, race and certain comorbidities are associated with being correctly diagnosed.

There were 20,061 patients in the study, and 7,575 were correctly diagnosed with prediabetes. Only 37% of the patients were diagnosed with prediabetes or impaired fasting blood glucose. Of those, 93% qualified by HbA1c levels.

Having obesity or overweight, being female, of Asian race, and living with comorbidities including lipid disorders and conditions requiring steroids

were linked to a correct diagnosis of prediabetes. Other factors, such as being male, Black and having comorbidities requiring immunosuppressants, antineoplastics and iron replacements were negatively correlated with a correct prediabetes diagnosis.

"Overall, this research reveals inherent biases that health care providers might have when diagnosing prediabetes and serves as a call for reflection within the provider's practice," Nguyen said.

Identification of Four New Glucotypes During the First Year After Type 1 Diabetes Onset Using Continuous Glucose Monitoring Metrics

Current markers of β-cell function poorly reflect glucose homeostasis after diabetes onset, mainly because of the lack of integration of parameters of insulin sensitivity and β-cell responsiveness to glucose. Recently, the widespread use of continuous glucose monitoring (CGM) helped stratify glucose control in patients with long-term diabetes in new clinically relevant glucotypes. In our DIATAG study, we investigated how CGM metrics may help to segregate patients with new-onset type 1 diabetes (T1D) entering or not in partial remission (PR).

We collected data from 66 pediatric patients with T1D (10.4±4.7 yo) during the first year after diabetes onset (Δ). Clinical parameters (i.e., A1C, insulin daily dose, insulin-dose adjusted A1c [IDAA1C]) and CGM data were collected at Δ+3, +6, +9, +12 months (n=168, 57% remitters [IDAA1C <9]). A panel of 46 CGM metrics was calculated on an hourly and daily basis using iglu package (1). Using unsupervised hierarchical clustering based on daily CGM metrics and clinical parameters, we identified four clusters of glucose metrics that differed from each other ($p<0.05$).

Cluster 1 was characterized by an increased glucose stability (coefficient of variation [CV] 32±5%) within time in target (TIT [63-140 mg/dL], 83±6%) with 9% of sensor values in 63-70 mg/dL range in the early morning period. Cluster 2 exhibited a progressive decrease of TIT (60±14%) and an increase of target above range (TAR [>180 mg/dL], 20±9%) especially during the day while target in range (TIR [70-180 mg/dL]) was nearly equivalent to Cluster 1 (80±8%). Notably, CV remained low (32±5%) with little time spent below range (TBR [<70 mg/dL], 5±2%). Cluster 3 demonstrated a net increase of CV during all the nycthemere (46±7%) concomitantly to an increase of TBR (14±7%). Interestingly, TIT and TAR remained close to values from Cluster 2 (55±11%; 23±10%).

Finally, Cluster 4 demonstrated major hyperglycemias (TAR, 55±13%) with increased CV (47±9%) and decreased TBR (8±6%). Interestingly, clustering allowed clinically relevant segregation of intermediate values of IDAA1C (i.e., 7.5-10) between Cluster 2 and Cluster 3, independently of the remission status. Moreover, participants at Δ+3 months distributed across all clusters (with respectively 38% in Cluster 1, 26% in Cluster 2, 29% in Cluster 3 and 7% in Cluster 4) highlighting the usefulness of CGM in characterizing disease heterogeneity from diabetes onset. In our study, a combination of CGM metrics and clinical parameters unraveled key clinical milestones of glucose homeostasis and remission status during the first year of T1D.

« SESSION-7 »

Dilemmas in Diabetes Mellitus in Youth

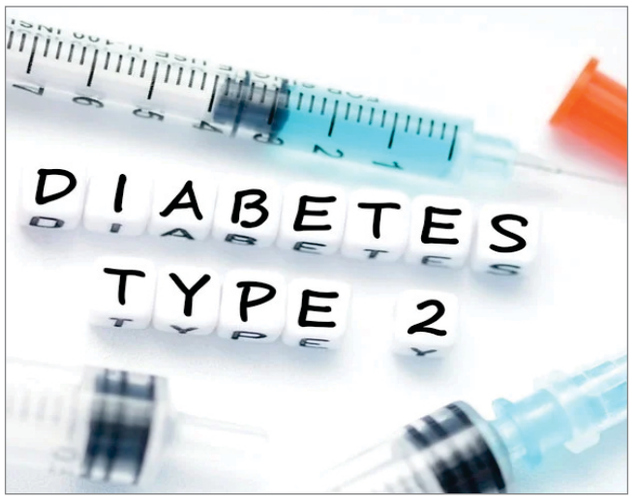
Disrupted Circadian Rhythm in Catecholamines in Youth-Onset Type 2 Diabetes

In healthy, normal - weight adults there is a circadian rhythm in blood pressure (BP) and plasma catecholamines (epinephrine and norepinephrine): BP and the levels of norepinephrine and epinephrine decline during sleep, followed by a rapid increase during the early morning hours. Studies in adults with Type 2 diabetes (T2D) show blunted reductions in BP and plasma catecholamine levels during sleep that are associated with increased risks for heart failure, stroke, myocardial infarction, and sudden death. In this study, we explored if the circadian rhythm in catecholamines is disrupted in youth-onset T2D. We hypothesized that increased sympatho-adrenal activity during sleep differentiates youth with T2D from non-diabetic overweight/obese and lean youth of comparable age, pubertal status, and ethnicity. To that end, we measured urine catecholamines in fasting – morning-spot urines and 24-hour urine samples.

56 non-diabetic adolescents with overweight/obesity ("obese"), 42 adolescents with T2D ("T2D"), and 43 normal-weight controls ("lean"); aged 12-21 years, were studied. None was diagnosed with hypertension, and none was on antihypertensive treatment. Weight, height, BMI, BMI%, and BP were extracted from medical charts. Body fat percent (BF%) was measured by TANITA. Stress levels were assessed using PHQ-2 and PHQ-9 questionnaires. Fractionated free urine catecholamines (epinephrine, norepinephrine, and dopamine) were analyzed by liquid chromatography/tandem mass spectrometry (LC/MS-MS) in both spot and 24-hour urines, normalized to urinary creatinine. The ratio of fasting morning urine catecholamines to 24-hour urine catecholamines was calculated to assess circadian variation in catecholamines. Group differences were assessed by Kruskal-Wallis or ANOVA.

Groups were comparable for age (obese 14.8 ± 1.9; T2D 15.7 ± 2.1 and lean 14.9 ± 1.9-yr), pubertal status, and ethnicity. Obese youth with and without T2D were predominantly female (T2D, 28 F, 14 M; obese 33 F, 23 M; lean, 17 F, 26 M); those with T2D had highest BF% (obese 37.3 ± 9.5; T2D 42.9 ± 9.9; lean 20.1 ± 6.3 %; p=2.58-22) and systolic blood pressure (obese 115.36 ± 11.54; T2D 127.83 ± 12.08 and lean 111.65 ± 9.13 mmHg; p=5.49-10). Fractionated free urine catecholamines (epinephrine, norepinephrine and dopamine) were comparable across groups in 24-hour urines. However, fasting morning epinephrine levels and the ratio of fasting morning/24-hour epinephrine were higher in T2D (p=0.0035, and p=0.035, respectively) than in either lean or nondiabetic youth with obesity. There were no differences in morning urine catecholamines between lean controls and non-diabetic youth with obesity.

Our **results** suggest a disrupted circadian rhythm in catecholamines in youth-onset T2D, with a blunted overnight fall in epinephrine levels. Higher levels of epinephrine levels at night in youth with T2D might be associated with, or predispose to, hypertension and long-term cardiovascular complications.



Branched-Chain Amino Acid and Tryptophan Metabolism and the Pathogenesis of Youth-Onset Type 2 Diabetes Mellitus (T2D)

We have previously demonstrated that insulin resistance (IR) in youth is associated with elevated levels of branched-chain amino acids (BCAAs). BCAAs compete with aromatic amino acids (AAA) including tryptophan, the precursor of serotonin, for uptake into β-cells and other tissues via the large neutral amino acid transporter. Serotonin has been reported to increase β-cell mass and glucose-dependent insulin secretion. In this study we have explored how BCAA, tryptophan (one of the AAA), and a subset of their metabolites are modulated in youth-onset T2D. Based on our prior studies in neuronal BCAA metabolism, we hypothesized that elevated BCAA could induce diversion of tryptophan metabolism towards production of kynurenine rather than serotonin in youth with T2D. To test this, we analyzed 24-hour urine samples and compared levels of byproducts of BCAAs and tryptophan metabolism in obese youth with T2D with those in non-diabetic obese and lean youth of comparable age, pubertal status and ethnicity.

56 non-diabetic adolescents with overweight/obesity ("obese"), 42 adolescents with T2D ("T2D"), and 43 normal weight controls ("lean"), ages 12-21 years-old were studied. Weight, height, BMI, BMI% were extracted from medical charts. Body fat percent (BF%) was measured by TANITA. We also measured metabolites derived from BCAA catabolism, including the branched-chain ketoacids (BCKAs), and tryptophan metabolism, including intermediates of the serotonergic and kynurenine pathways, in spot and 24-hour urine samples by liquid chromatography/tandem-mass spectrometry (LC/MS-MS). Levels were normalized to urine creatinine. Group differences were assessed by Kruskal Wallis or ANOVA.

Groups were comparable for age (obese 14.8 ± 1.9; T2D 15.7 ± 2.1 and lean 14.9 ± 1.9-yr), pubertal status, and ethnicity. Youth with T2D were predominantly female (T2D, 28 F, 14 M; obese 33 F, 23 M and lean, 17 F, 26 M), and had highest BF% (obese 37.3 ± 9.5; T2D 42.9 ± 9.9; lean 20.1 ± 6.3 %; p=2.58-22). In 24-hour urine samples, BCKAs, tryptophan, and kynurenine levels were higher in T2D (p=0.0002, p= 0.0045 and p= 0.00009 respectively) than in either lean controls or nondiabetic youth with obesity; in contrast, there were no differences between lean controls and non-diabetic youth with obesity. The levels of 5-HIAA, the principal metabolite of serotonin, were comparable across groups; however, the ratio of kynurenine/tryptophan was higher (p= 0.0112) in youth with T2D and the ratios of 5-HIAA/tryptophan (p=0.027) and 5-HIAA/Kynurenine (p=0.0067) were lower compared to the other two groups. Those ratios were comparable between lean controls and non-diabetic youth with obesity.

Increased BCKAs are accompanied by diversion of tryptophan metabolism from the serotonin pathway to the kynurenine pathway, suggesting perturbations in both BCAA and AAA metabolism in youth-onset T2D. These alterations could contribute to development of beta-cell dysfunction and progression to T2D in youth.

Diabetic Retinopathy and Diabetes-Related Renal Disease, Either Isolated or Both Associated, and the Impact on the 10-Year Risk of Cardiovascular Disease: Are We Dealing with Similar Conditions?

This paper was presented by Ms. Clara Maraschin, from the UMS Universidade Federal Do Rio Grande do Sul.

When we consider the presence of retinopathy (DR) and diabetes-related renal disease (DRD), isolated or both associated, and the impact on the 10-year risk of cardiovascular disease, one important question is risen: are we dealing with similar conditions?

It is known that the presence of those diabetes microvascular complications may result in worse quality of life, disability and premature death, mainly due to cardiovascular disease. Despite the great advances in prevention and treatment options, diabetes remains a major ASCVD risk factor. In this context, there has been a growing focus on diabetes-related complications and their impact on chronic outcomes.

This study aims to assess the association between the presence of DR, DRD and the 10-year risk of ASCVD in patients with diabetes. Patients' data were extracted from medical records between 2019 to 2020 and the patients were stratified into 4 different groups: G1(no diabetes-related complications); G2 (RD only); G3 (DRD only); G4 (presence of both RD and DRD).

Among patients with type II diabetes mellitus, the presence of specific microvascular complications affects the 10-year cardiovascular risk differently, and the renal involvement seems to be associated with a greater theoretical cardiovascular risk when compared to the presence of RD alone.

Study Finds Strong Association Between Prediabetes and Heart Attack Risk

Prediabetes appears to be a strong independent risk factor for heart attacks, according to a new study presented at ENDO 2022.

Prediabetes is a condition in which blood glucose levels are higher than normal, but not high enough to be considered diabetes. People with prediabetes are more prone to develop diabetes. While diabetes is known to cause serious health conditions such as heart attacks, stroke and kidney problems, the link between prediabetes and heart problems has not been well established, according to study lead author Geethika Thota, M.D., of Saint Peter's University Hospital/Rutgers Robert Wood Johnson Medical School in New Brunswick, N.J.

"Our study serves as a wake-up to everyone to shift the focus to managing prediabetes, not just diabetes," Thota said. "Based on our findings, we encourage everyone to make lifestyle changes, follow a healthy diet and regularly exercise for at least 150 minutes each week in patients with prediabetes to decrease the risk of heart attacks."

The researchers analyzed data from 1.79 million hospitalizations of patients who had a heart attack. Of these patients, 1% had prediabetes. After adjusting for risk factors for heart disease including age, sex, race, family history of heart attack, high blood pressure, high cholesterol, diabetes, smoking and obesity, prediabetes was associated with 25% increased odds of a heart attack, compared with patients without prediabetes. Those with prediabetes also were at 45% increased odds for having percutaneous intervention (a heart treatment to open blocked blood vessels) and almost double the risk of having heart bypass surgery.

"Our findings reinforce the importance of early recognition by screening and early intervention of prediabetes by lifestyle changes and/or medications to decrease the risk of cardiovascular events," Thota said.

Sex Differences in Body Composition and Incident Diabetes Across BMI Categories in Older Versus Younger Adults

Body composition often changes with age. While body mass index (BMI) is used to define obesity, the degree to which BMI accurately or consistently reflects fatness in older versus younger adults remains unclear. Importantly, it is uncertain whether diabetes risk is similar for older versus younger adults within BMI-defined categories.

We evaluated the relationship of older (≥65 years) versus younger age (<65 years) to dual-energy X-ray absorptiometry (DXA)-derived body composition measures and incident diabetes, stratified by BMI-defined categories for non-overweight/non-obese (<25 kg/m^2), overweight (25-29.9 kg/m^2) and obesity (≥30 kg/m^2).

Design: Participants without diabetes at first DXA visit in the Baltimore Longitudinal Study of Aging were included. Linear regression models were used to investigate the association of age categories to body composition at baseline, and Cox proportional hazard models were used to study the relationship of age categories to incident diabetes, within BMI categories for men and women. Diabetes was defined based on self-reported history, medication use, and/or ADA diagnostic criteria (fasting or 2-hour OGTT glucose levels).

A total of 993 men (n=463 older, n=530 younger) and 1109 women (n=385 older, n=724 younger) were examined. Comparing older versus younger participants, body weight was significantly lower across all BMI categories for both men and women (all p<0.05). Percent total fat mass (%TFM) and fat mass/lean mass ratio (FM/LM) were significantly higher in older versus younger men across all BMI categories and in non-overweight/non-obese women. Among men, in multiple regression analyses adjusting for race, education, height and weight, the relationship (β±SE) of older versus younger age (reference) to %TFM remained significant (non-overweight/non-obese: 1.84 ± 0.59, overweight: 2.60±0.47, obese: 1.81± 0.87; all p<0.05), as did the relationship to FM/LM, across all BMI categories. Among women, the relationships of older versus younger age (reference) to %TFM and FM/LM remained significant for non-overweight/non-obese women. Over a median follow-up of 7.3 years (IQR=1.9-16.6), there were 165 incident cases of diabetes. Older obese men had an almost three-fold higher risk of developing diabetes than younger obese men (HR=2.72 [95%CI: 1.12, 6.63]), accounting for race, education, height, weight and %TFM. Among women, no differences by age group in incident diabetes were observed. Conclusions: In our study, sex differences were observed in the relationship of older versus younger age to several measures of body composition, suggesting greater relative fat mass with aging, particularly in men.

Further, our results suggest that BMI-defined categories for overweight and obesity do not fully account for changes in fat mass with aging and that the risk for diabetes is significantly greater for older compared to younger obese men. Further studies are needed to investigate the optimal BMI thresholds that predict diabetes risk in older adults.

Study Links Diabetes and Worse Outcomes in Long-Term Survivors of Metastatic Breast Cancer

Women who are longer-term survivors of metastatic breast cancer may have a worse survival rate if they have diabetes and poorly controlled blood sugar levels, according to a new study presented at ENDO 2022.

This is the first study to specifically examine the effect of blood sugar control on cancer outcomes in patients with advanced breast cancer, according to lead researcher Y.M. Melody Cheung, M.D., of Brigham and Women's Hospital, Harvard Medical School in Boston, Mass.

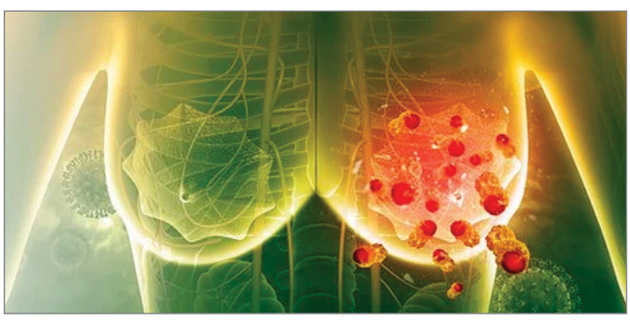
To date, there has been little research conducted on the effects of diabetes, and in particular, the impact of poor blood sugar control on advanced breast cancer outcomes. Existing studies have primarily focused on patients with early rather than advanced cancer.

Researchers studied 488 patients with metastatic breast cancer. Half had diabetes. The study found that overall survival at five years was similar between the two groups. However, amongst those that survived at least 8 years after their cancer diagnosis, survival for those without diabetes was better than those with diabetes (87% vs. 67% at 10 years). In these longer-term survivors, survival was also better among those with good blood sugar control compared with those with poor blood sugar control (83% vs. 63% at 10 years).

"Our findings suggest that in patients with breast cancer who have a relatively good prognosis despite their cancer diagnosis, a more proactive management of blood sugar may lead to a longer lifespan," Cheung said.

"These findings are important as they suggest that diabetes treatment and blood sugar goals should be tailored specifically to patients even with advanced cancer based on their projected prognosis," she added.

"It remains uncertain whether control of blood sugars in patients with diabetes and breast cancer can improve the outcomes of the cancer itself," Cheung said. "In some instances, blood sugar control may not be strongly pursued by doctors, especially in cases where the cancer is advanced, and strict diabetic control may be considered overly burdensome for patients. A link between poor blood sugar control and worse cancer outcomes may modify the way doctors treat diabetes in patients with advanced breast cancer."



« SESSION-8 »

Should Weight Management be the Primary Treatment Goal for Type 2 Diabetes

Phase 1, Randomized, Controlled Trial of GFB-024, A Once-Monthly CB1 Inverse Agonist, in Healthy Overweight and Obese Participants and in Participants with Type 2 Diabetes Mellitus

This paper was presented by Dr. Sanela Bilic, PharmD at Vanadro.

Evidence from nonclinical studies suggests a role of cannabinoid-1 receptor (CB1) in the development of diabetic nephropathy (DN). Kidney CB1 expression is upregulated in podocytes and tubular cells in murine models of obesity and diabetes mellitus (DM).

Inhibition by CB1 inverse agonists has been shown to ameliorate diabetes-induced albuminuria, inhibit kidney fibrosis and inflammation, and prevent podocyte dysfunction. Mouse models of DM have shown that genetic deletion of CB1 in podocytes or proximal tubular cells protects against glomerular and tubular dysfunction. GFB-024 is a recombinant humanized monoclonal antibody functioning as a CB1-specific inverse agonist.

Pharmacodynamic studies demonstrated that GFB-024 protects human podocytes in vitro. Targeting the CB1 pathway with GFB-024 is a potentially novel approach to protecting podocytes from injury in patients with CB1-associated DN. In a phase 1, randomized, double-blind, placebo-controlled single ascending dose

(SAD) trial, we evaluated the safety, tolerability, pharmacokinetics (PK), and immunogenicity of GFB-024 in up to 56 healthy overweight and obese (BMI 25 – 40 kg/m^2) participants. A total of 38 subjects have completed 5 cohorts in the SAD, receiving single doses of 5 mg to 300 mg administered subcutaneously.

GFB-024 was well tolerated, and there were no dose-limiting adverse effects. PK exposures achieved in the trial exceeded the estimated efficacious exposure, based on four different in vitro activity assays. Absorption was prolonged with flat exposure over the first 7 days, with a Tmax ranging from approximately 4-7 days. Elimination half-life was approximately 12-13 days, with exposures remaining in the estimated efficacious range at 28 days for all but the lowest dose tested.

In **summary**, GFB-024 was safe and well tolerated following single doses of up to 300 mg. PK analysis demonstrated potentially efficacious exposure, a prolonged absorption phase, and elimination half-life compatible with once-monthly dosing.

« SESSION-9 »

Tech Check for Diabetes: Use Technologies in the Management of Persons with Diabetes

Deep Learning-Based Voice Screening Technique for Cystic Fibrosis Related Diabetes

Cystic fibrosis-related diabetes (CFRD) is a unique type of diabetes that is associated with significantly increased morbidity and mortality in both children and adults with cystic fibrosis (CF). The prevalence of CFRD progressively increases with age such that more than half of adults with CF develop CFRD. Early diagnosis and treatment are associated with improvements in body weight and pulmonary function, reduction in the frequency of pulmonary exacerbations, and improved overall survival. Since patients with CFRD may present with no symptoms, screening is recommended starting from the age of 10 years with an annual oral glucose tolerance test (OGTT). Especially during the COVID-19 pandemic, requiring an in-person clinic visit can be challenging, which may lead to a delayed diagnosis of CFRD.

The purpose of this project was to develop a state-of-the-art technique to detect changes in glucose levels of patients with CF by developing a deep learning-based audio classification tool. Preliminary work by our group suggested that voice characteristics could distinguish between patients with CFRD patients and patients with CF but without CFRD. We hypothesize that high blood glucose levels may cause laryngeal soft tissue swelling leading to changes in voice characteristics. We performed a prospective cross-sectional study in adult patients with CF recruited from Emory CF Clinic from March to December 2021. We recorded 5-second voice samples of a sustained /a/vowel via a portable digital microphone. The spectrogram was extracted via the Mel frequency cepstral coefficient. The training to test the dataset ratio was 80:20. 20% of the training dataset were randomly selected to serve as a validation dataset. We designed a convolutional neural network (CNN) architecture for CFRD patients' voice classification.

There was a total of 100 subjects consisting of 43 patients with CFRD and 57 patients with CF without diabetes. The male to female ratio was approximately 60:40 in both groups. Patients with CFRD had similar mean age and mean BMI to patients without CFRD. There was a significantly higher point of care glucose level in CFRD patients. The mean duration of a CFRD diagnosis was 9 years and the mean HbA1c level was 7.26 in the CFRD group. The performance of the VGG model CNN classifier achieved 98.7% and 94.92% accuracy on training and validation datasets, respectively. On the test dataset, the model achieved 73.53% sensitivity 69.77% specificity and 71.43% accuracy.

We found a deep learning-based audio screening tool for CFRD could be potentially used as an alternative tool for screening in the CF community.

A convolutional neural network algorithm demonstrated high sensitivity and specificity to adequately differentiate between patients with and without CFRD. Larger prospective studies are required to test this technology in patients with every form of diabetes.

Combating Therapeutic Inertia: Project ECHO for Diabetes Improves Primary Care Providers' Comfort and Use of Diabetes Medication and Technology

Despite newer diabetes medications and technology being available, therapeutic inertia persists and there are more people living with "uncontrolled" diabetes than meeting A1c targets. Here we evaluate how the ECHO© model for diabetes management changed prescribing practices among participating primary care providers (PCPS).

Three unique diabetes ECHO programs evaluated comfort or perception of prescribing practice changes for local community PCPs (n=74) in four regions (Illinois, District of Columbia, New Mexico, and Washington). One site representing two regions collected pre- and post-program participant surveys (n=45) while two sites collected post-program surveys only (n=29), in which respondents reported perceptions of changes resulting from participation in ECHO.

Participants reported their use of technology (professional and personal continuous glucose monitoring (CGM) and insulin pumps) and medications (insulin and non-insulin).

On a 4-point Likert scale, PCPs' (n=45) average self-reported prescription use for newer diabetes medications with cardiovascular indications increased from 3.07 (sometimes) to 3.84 (sometimes-always).

« SESSION-10 »

Management of Hyperglycaemia in Hospitalized Patient in Non-Critical Care Settings: An Endocrine Society Clinical Practice Guidelines

New Guideline for In-Hospital Care of Diabetes Says Use CGMs

Goal-directed glycemic management - which may include new technologies for glucose monitoring - for non-critically ill hospitalized patients who have diabetes or newly recognized hyperglycemia can improve outcomes, according to a new practice guideline from the Endocrine Society.

Even though roughly 35% of hospitalized patients have diabetes or newly discovered hyperglycemia, there is "wide variability in glycemic management in clinical practice," writing panel chair Mary Korytkowski, MD, from the University of Pittsburgh, Pittsburgh, Pennsylvania, said during a press briefing at ENDO 2022.

"These patients get admitted to every patient service in the hospital, meaning that every clinical service will encounter this group of patients, and their glycemic management can have a major effect on their outcomes. Both short term and long term."

This guideline provides strategies "to achieve previously recommended glycemic goals while also reducing the risk for hypoglycemia, and this includes inpatient use of insulin pump therapy or continuous glucose monitoring (CGM) devices, among others," she said.

It also includes "recommendations for preoperative glycemic goals as well as when the use of correctional insulin - well known as sliding scale insulin - may be appropriate" and when it is not.

The document, which replaces a 2012 guideline, A multidisciplinary panel developed the document over the last 3 years to answer 10 clinical practice questions related to management of non-critically ill hospitalized patients with diabetes or newly discovered hyperglycemia.

Use of CGM Devices in Hospital

The first recommendation is:

"In adults with insulin-treated diabetes hospitalized for noncritical illness who are at high risk of hypoglycemia, we suggest the use of real-time [CGM] with confirmatory bedside point-of-care blood glucose monitoring for adjustments in insulin dosing rather than point-of-care blood glucose testing alone in hospital settings where resources and training are available." (Conditional recommendation. Low certainty of evidence).

Although CGMs are approved by the US Food and Drug Administration (FDA) in the outpatient setting, and that's becoming the standard of care there, they are not yet approved for in-hospital use. However, as previously reported, the FDA granted an emergency allowance for use of CGMs in hospitals during the COVID-19 pandemic.

That was "when everyone was scrambling for what to do," Korytkowski noted. "There was a shortage of personal protective equipment and a real interest in trying to limit the amount of exposure of healthcare personnel in some of these really critically ill patients for whom intravenous insulin therapy was used to control their glucose level."

On March 1, the FDA granted Breakthrough Devices Designation for Dexcom CGM use in the hospital setting.

The new guideline suggests CGM be used to detect trends in glycemic management, with insulin dosing decisions made with point-of-care glucose measure (the standard of care).

To implement CGM for glycemic management in hospitals, Korytkowski said, would require "extensive staff and nursing education to have people with expertise available to provide support to nursing personnel who are both placing these devices, changing these devices, looking at trends, and then knowing when to remove them for certain procedures such as MRI or radiologic procedures."

"We know that not all hospitals may be readily available to use these devices," she said. "It is an area of active research. But the use of these devices during the pandemic, in both critical care and non-critical care setting has really provided us with a lot of information that was used to formulate this suggestion in the guideline."

The document addresses the following areas: CGM, continuous subcutaneous insulin infusion (CSII) pump therapy, inpatient diabetes education, prespecified preoperative glycemic targets, use of neutral protamine Hagedorn (NPH) insulin for glucocorticoid or enteral nutrition-associated hyperglycemia, noninsulin therapies, preoperative carbohydrate-containing oral fluids, carbohydrate counting for prandial (mealtime) insulin dosing, and correctional and scheduled (basal or basal bolus) insulin therapies.

Nine Key Recommendations

Korytkowski identified nine key recommendations:

- Continuous glucose monitoring systems can help guide glycemic management with reduced risk for hypoglycemia
- Patients experiencing glucocorticoid- or enteral nutrition-associated hyperglycemia require scheduled insulin therapy to address anticipated glucose excursions
- Selected patients using insulin pump therapy prior to a hospital admission can continue to use these devices in the hospital if they have the mental and physical capacity to do so with knowledgeable hospital personnel
- Diabetes self-management education provided to hospitalized patients can promote improved glycemic control following discharge with reductions in the risk for hospital readmission. "We know that is recommended for patients in the outpatient setting but often they do not get this, "she said. "We were able to observe that this can also impact long-term outcomes"
- Patients with diabetes scheduled for elective surgery may have improved postoperative outcomes when preoperative A1c is ≤ 8% and preoperative blood glucose < 180 mg/dL. "This recommendation answers the question 'Where

should glycemic goals be for people who are undergoing surgery?"

- Providing preoperative carbohydrate-containing beverages to patients with known diabetes is not recommended
- Patients with newly recognized hyperglycemia or well-managed diabetes on noninsulin therapy may be treated with correctional insulin alone as initial therapy at hospital admission. Some noninsulin diabetes therapies can be used in combination with correction insulin for patients with Type 2 diabetes who have mild hyperglycemia
- Correctional insulin - "otherwise known as sliding scale insulin" - can be used as initial therapy for patients with newly recognized hyperglycemia or type 2 diabetes treated with noninsulin therapy prior to hospital admission
- Scheduled insulin therapy is preferred for patients experiencing persistent blood glucose values > 180 mg/dL and is recommended for patients using insulin therapy prior to admission

The Guideline Writers' Hopes

"We hope that this guideline will resolve debates" about appropriate preoperative glycemic management and when sliding insulin can be used and should not be used, said Korytkowski.

The authors also hope that "it will stimulate research funding for this very important aspect of diabetes care, and that hospitals will recognize the importance of having access to knowledgeable diabetes care and education specialists who can provide staff education regarding inpatient glycemic management, provide oversight for patients using insulin pump therapy or CGM devices, and empower hospital nurses to provide diabetes (self-management) education prior to patient discharge."

Claire Pegg, the patient representative on the panel, hopes "that this guideline serves as the beginning of a conversation that will allow inpatient caregivers to provide individualized care to patients — some of whom may be self-sufficient with their glycemic management and others who need additional assistance."

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