DOI: 10.1111/pedi.13233

MISCELLANEOUS

ISPAD WILEY

ISPAD roving reporters 2020

PLENARY 1: ADVANCES IN DIABETES

Type 1 diabetes (T1D) progresses through stages. Those at increased genetic risk progress to alterations in immune regulation leading to an imbalance between T regulatory and T effector cells and the development of pancreatic autoantibodies. In the next stage individuals with T1D have asymptomatic abnormal glucose tolerance, which then progresses to symptomatic clinical diabetes, and finally long-standing T1D. All individuals with stage 1 T1D, characterized by at least two pancreatic autoantibodies, will progress to clinical T1D over 15–20 years. Teplizumab, a monoclonal antibody that binds CD3 on the T-cell receptor, has been shown to delay the onset of Stage 3 clinical T1D in patients with autoantibodies and abnormal oral glucose tolerance test (OGTT). Ongoing TrialNet studies are focusing on the use of hydroxychloroquine and abatacept to intercede in the progression of T1D. However, to date, prevention and cure of T1D have remained elusive and no therapies have produced robust, durable effects on inducing immune tolerance or preserving insulin secretion.

Suboptimal glycemic control, weight gain, and severe hypoglycemia are areas of unmet clinical need in T1D care. Severe hypoglycemia is associated with decreased quality of life, fear of hypoglycemia and resulting suboptimal control, cognitive decline, and increased mortality. Despite these risks, approximately half of people with T1D do not fill prescriptions for glucagon and 50% of trained caregivers failed to administer intramuscular glucagon in a simulated episode of severe hypoglycemia. In studies, nasal glucagon 3 mg successfully raised blood glucose values in all patients and was successfully administered by 94% of trained caregivers and 93% of untrained acquaintances.

Glucagon-like peptide-1 (GLP-1) agonists are typically prescribed for Type 2 diabetes (T2D), however evidence showing reduced postprandial hyperglycemia and hepatic glucose output suggests the potential use of these agents as adjunctive therapy in T1D. In adults with T1D, the use of liraglutide resulted in sustained hemoglobin A1c (A1c) reductions of approximately 0.5% and up to 4 kg of weight loss. Despite these potential benefits, use has been limited by increased rates of hypoglycemia and ketotic hyperglycemia. Similarly, sodium glucose co-transporter 2 inhibitors (SGLT2i), which inhibit renal glucose reabsorption, have been associated with improvements in A1c and blood pressure, weight loss, and decreased urine microalbumin levels. Despite these potential benefits, their use in T1D has been limited by a 2–4 fold greater risk for diabetic ketoacidosis (DKA).

SYMPOSIUM 1: DIABETES PREVENTION

T1D progresses through stages of disease, beginning with genetic risk conveyed by HLA haplotype followed by immune activation leading to Stage 1 (normal blood glucose levels with ≥2 antibodies), abnormal glucose tolerance in Stage 2, and then symptomatic clinical T1D in Stage 3. Trials have sought to identify metabolic markers that predict progression through the stages of T1D to guide the development of prevention strategies. C-peptide levels during an OGTT in individuals with Stage 2 T1D predict progression to Stage 3 up to 6.6 years in advance. Interventional trials using rituximab (anti-CD20), teplizumab (anti-CD3), abatacept (CTLA4-Ig), anti-thymocyte globulin (ATG) have shown varying degrees of success in preserving insulin production. One of the most successful studies to date showed that 2-week treatment with teplizumab delayed the onset of T1D by a mean of 2 years in those with Stage 2 T1D. Other promising areas of research include a vaccine against the Coxsackievirus, an enterovirus associated with the development of T1D, and the use of polyamine a-difluoromethylornithine (DFMO) which inhibits cytokine-induced inflammatory response in β-cells.

Despite advances in our understanding of disease pathophysiology, interventions to date have not provided robust durable effects leading to T1D remission or cure. Paradigm shifts have brought about increased emphasis on personalized medicine and understanding T1D as a heterogenous syndrome. With interventional trials delayed due to the COVID-19 pandemic, research has focused on understanding different "endotypes," characterized by individual differences in immune dysregulation, genetic and metabolic markers, β-cell health, and stages of disease progression. Future studies will seek to combine immuno-modulating agents and tailor interventions according to endotype. There has also been a call to focus on individuals in earlier stages of T1D and to consider the use of earlier endpoints, such as C-peptide levels and immune markers rather than disease progression, that will lead to more rapid results from interventional studies.

SYMPOSIUM 2: ADVANCES IN DIABETES

Diabetes technology- smart pens, insulin pumps, continuous glucose monitors (CGM), and hybrid closed loop insulin delivery systems- is being increasingly used to improve diabetes management. However, currently there is a technology paradox: despite the increasing use of diabetes technologies, most people with T1D do not reach glycemic targets. Maintaining good metabolic control is challenging and

laborious. Diabetes burn-out has been reported by both patients and diabetes healthcare professionals alike due to increase in time required to interpret downloads from pumps and CGM. Future developments in diabetes technology will seek to increase automatization of diabetes management to reduce the burden while simultaneously improving diabetes outcomes.

Hybrid closed loop systems automate insulin delivery by using an algorithm to integrate CGM glucose data with insulin delivery through an insulin pump. These systems are considered hybrid closed-loop, rather than true closed loop, because although basal rates can be adjusted and automated correction factors delivered for hyperglycemia, the user is still required to deliver boluses at mealtime and to adjust for activity and other factors impacting glycemia. Two hybrid closed-loop systems have already been cleared by the FDA for commercial use and many are already using it around the globe with significant improvements in time in range without increases in adverse effects such as severe hypoglycemia and DKA.

While there are several commercially available systems, people with T1D are increasingly turning to the rapid innovation afforded by open-source software development. "Do-It-Yourself" (DIY) closed-loop insulin delivery systems were developed by individuals within the T1D community. One such system, "Loop" an open-source app that runs on an iPhone, is used worldwide by over 9000 people and the number of DIY users continues to increase. In an effort to commercialize these DIY systems and increase access, Tidepool is seeking to develop a regulated and supported commercial product while still harnessing the DIY spirit of fast-paced innovation. Benefits to a commercially available device include clearance from regulatory bodies, the ability to prescribe these systems and access them through the App store, and the ability to develop training and support systems for patients and providers.

SYMPOSIUM 3: ACCESS TO DIABETES MANAGEMENT

Access to affordable diabetes care, supplies, and insulin therapy remains a significant problem in low and middle income countries (LMIC) where healthcare systems are often clustered in urban areas and structured to meet acute, rather than chronic, healthcare needs. The World Health Organization (WHO) goal is to ensure 80% availability of affordable insulin worldwide, however recent studies show inequities and inefficiencies in the insulin market that have prevented attainment of this goal, particularly in rural areas. The costs of insulin and diabetes supplies vary widely among counties and are impacted by manufacturing costs, price paid by distributors, taxes, and whether insulin is acquired through the government or the private sector. Ensuring that insulin is on the national essential medication lists and that it is included in the standard treatment guidelines for T1D and T2D, better assessing the needs of each country through national registries documenting the prevalence of T1D and T2D, developing cost-effective strategies to procure and distribute essential supplies, removing barriers to competition among manufactures, and improving cost transparency so as to limit mark-ups are essential steps in improving diabetes care and outcomes in LMIC.

Record high levels of forced migration, humanitarian crises resulting in protracted refugee situations, and additional challenges posed by the COVID-19 pandemic have further strained already struggling healthcare systems in LMIC. The Boston Declaration of 2019, signed by 64 signatories from more than 40 international organizations outlined four major areas for improvement in T1D care during humanitarian crises: (1) unified and strengthened advocacy, (2) universal access to insulin and other essential medications and supplies, (3) establishing a unified set of clinical and operational guidelines, and (4) improving data and surveillance. Diabetes is a crisis within a crisis that represents an urgent need for advocacy, approaches to ensure delivery of essential care and mediations, and surveillance systems to monitor and drive progress to ensure that better access to supplies will ultimately lead to better outcomes.

SYMPOSIUM 4: FOOD AND FAT

Although approximately 60% of glycemic variability is explained by carbohydrate intake and up to 30% is explained by dietary fat, typically only carbohydrates and blood glucose levels are used to calculate rapid acting insulin doses. This model fails to acknowledge the impact of fat, protein, glycemic index, alcohol, exercise, and many other factors on blood glucose levels.

Dietary fat and protein both lead to late postprandial hyperglycemia and have an additive effect when eaten together. Fat slows gastric emptying and promotes insulin resistance in the liver and skeletal muscles, collectively leading to late postprandial hyperglycemia. There are no clear guidelines on what constitutes a meal high in fat and/ or protein and how best to adjust insulin doses for those types of meals. However, it has been suggested that meals containing more than 30 g of fat may require 130% of the calculated insulin dose and are best delivered over 2–4 h with 60% given up front and the remaining 40% as an extended bolus for pump users or a second injection 1-h late for those using multiple daily injection therapy. Meals high in both fat and protein may require 160% of the calculated insulin dose and are best delivered over a similar distribution and duration of time.

The glycemic index (GI) ranges between 1 and 100, with higher numbers indicating a greater rise in blood glucose values after consumption. The GI is impacted by processing of foods and removal of fiber, food preparation, and food storage. High GI meals lead to a faster and more sustained post-prandial glycemic excursions. Although there is no strong evidence about how to best manage foods with varying GI, strategies for managing high GI foods include: bolusing more than 20 min before the meal, increasing the insulin dose, and using a so-called "super bolus" in which the pump user adds 1–4 h of basal insulin into the meal time bolus and then runs a temporary basal rate of zero.

PLENARY 2: DIABETES AND COVID

Diabetes was reported as a risk factor for more serious COVID-19 infections and complications early in the course of the pandemic.

With more data available, we have a better understanding of diabetes-specific risk factors in the setting of COVID-19 infection, including the type of diabetes, duration of diagnosis, glycemic control, and diabetes comorbidities. Large scale studies have shown either no change in the incidence of T1D, or even decreased incidence during the pandemic. However, there have been higher rates of DKA and severe DKA thought to be due to difficulty in accessing routine care, reduced availability of healthcare services, and fear of COVID-19. The pandemic has also highlighted underlying disparities in diabetes care. Consistent with trends among all people, rates of COVID-19 infection among people with T1D are higher in minorities. As compared to Caucasians, non-Hispanic Black and Hispanic people with T1D and confirmed COVID-19 infection were less likely to use CGM or insulin pump therapy and to have private insurance. Even after controlling for age, A1c, sex, and health insurance, non-Hispanic Black and Hispanic people with T1D with confirmed COVID-19 were more likely to develop DKA.

In April 2020 ISPAD launched an online COVID-19 survey that was answered by diabetes care team members at 215 diabetes centers in 75 countries worldwide. Twenty-two percent of respondents reported delays in T1D diagnosis and 35% reported shortages of diabetes supplies, including test-strips, insulin, continuous glucose monitor supplies, ketone strips, and insulin pump supplies. New onset T1D education was delivered face-to-face by 40% of respondents while 75% reported using phone, video, or app based education. Follow-up diabetes consultation was provided by phone or video in 50% of respondents. Similarly, although virtual healthcare has enabled diabetes care teams to continue to connect with patients and families, this has worsened the chasm between those who do and do not have access to the diabetes and technological tools needed for successful virtual care.

SYMPOSIUM 5: DIABETES AND PSYCHOLOGY

Many aspects of psychology are intimately linked to T1D care, including the emotional burdens of living with T1D and the impact of developmental stages on self-care and management. The emotional and behavioral needs of youth with T1D and their parents change as they grow and develop. Understanding a child's developmental stage and the associated emotional and behavioral challenges enables providers to better support youth and their parents. Diabetes distress, defined as the emotional response to living with T1D, and depression, a clinical diagnosis, are common in youth with T1D and often co-occur. Diabetes distress, but not depression, has been associated with suboptimal glycemic control. The causes of diabetes distress differ according to gender, however a perceived lack of understanding of the challenges of living with T1D among friends and family is a significant factor in both genders. Further evidence to determine the optimal timing and tools for screening for depression and diabetes distress and how to best implement these practices is needed.

Our understanding of the cognitive impact of the metabolic changes associated with T1D has evolved in the past decade. Whereas hypoglycemia was once thought to be primary cause of cognitive deficits and structural brain changes, studies have shown that early age at diagnosis (<4.7 years) has the greatest impact followed by hyperglycemia and resulting increases in oxidative stress, and DKA. Hypoglycemia if severe, prolonged, or occurring in the very young child can also have deleterious effects. Care teams should be aware of the feedback loop involving suboptimal glycemic control, neuronal injury, impaired executive function that ultimately contributes to difficulty adhering to T1D management.

SYMPOSIUM 6: DIABETES COMPLICATIONS

Diabetes complications continue to pose a significant threat to the lives of individuals with diabetes, their families, and society as a whole. Complications account for 80% of costs related to diabetes care before even considering the impact on productivity, quality of life, and mortality. Suboptimal glycemic control soon after diabetes diagnosis, younger age at diagnosis, and post-pubertal status all convey increased risk for the long-term development of microvascular complications. The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial assessed the efficacy of early treatment with angiotensin-converting enzyme inhibitors (ACEi) and statins in adolescents with T1D. Though these treatments failed to show utility for improving albumin creatinine ratio (ACR), this study has provided useful information about the risk of developing microvascular complications. Hypertension and ACR in the upper tertile of normal both independently predict the risk of nephropathy, cardiovascular disease, and progression of diabetic retinopathy. The use of ACEi for hypertension was shown to improve endothelial function and may slow the progression of diabetic retinopathy in those with elevated ACR.

Insights from a 4-year prospective single-center study of a multidisciplinary diabetes program in India highlighted the challenges of providing care in a high-volume center in which many patients have limited formal education and financial means. The median A1c was 8.3% and only 29% attained the target of <7%. The prevalence of hypertension among pediatric patients with T1D and T2D was 9.1% and 11.7%, retinopathy 10%–21% and 28%, nephropathy 13%–19% and 29% and neuropathy 5% and 10%, respectively.

SYMPOSIUM 7: OBESITY AND DYSLIPIDEMIA

Obesity is considered a state of "meta-inflammation," the proposed central mechanism connecting obesity to vascular complications. Dysfunction of the adipose tissue is manifested with a lower adiponectin/leptin ratio, which alters energy metabolism and worsens adiposity while also promoting endothelial damage. Body mass index (BMI) is the most standardized anthropometric biomarker used for estimation of body fat, however, it has low specificity for diagnosing obesity as it does not account for muscle mass and frame size. Wrist circumference presents as a novel, practical biomarker that has been correlated

with fasting insulin, blood pressure, and left ventricular hypertrophy in children with elevated BMI.

The pharmacologic treatments approved for severe obesity in children, orlistat, phentermine, and metformin, have low tolerability and efficacy with only a 0.32% reduction in BMI. Sleeve gastrectomy is more effective in achieving weight loss than lifestyle interventions and medications, resulting in 25%–30% weight loss after 3 years, and is also associated with resolution of T2D, dyslipidemia, and hypertension. After individualized consideration, adolescents with Class 2 obesity, BMI ≥35 kg/m2 or 120% of the 95th percentile, are candidates for bariatric surgery if they have comorbid conditions and those with Class 3 obesity, BMI ≥40 kg/m^2 or 140% of the 95th percentile, are candidates in the absence of comorbid conditions.

Dyslipidemia is very common in youth with both T1D and T2D and is a major modifiable risk factor for atherosclerotic CVD. ISPAD guidelines recommend the following targets in pediatric patients with diabetes: LDL-c < 100 md/dl, HDL-c > 35 mg/dl, TG < 150 mg/dl. Non-pharmacological therapies focus on lifestyle changes and improving glycemic control. Pharmacological therapy with a statin should be considered in patients >11 years old with an LDL-c persistently >130 mg/dl. Ezetimibe is approved in the US as an additive agent for lowering LDL-c in the pediatric population, or when statins are not tolerated. Patients with fasting TG 400–1000 mg/dl are at increased risk of pancreatitis, therefore treatment with fibrates is recommended.

PLENARY 3: OBESITY AND T2DM

Recent findings from the RISE study highlighted unique features of T2D in children. Insulin sensitivity is 50% lower in children than in adults of a similar BMI. Insulin secretion is higher in children than adults for every level of insulin sensitivity and C-peptide responses to glucose are 2–3 times greater in children than in adults. Metformin therapy improves insulin sensitivity and decreases insulin secretion in adults, but has a more modest effect in children. However, findings from the TODAY study show that metformin proved effective for glycemic control in 50% of children with T2D. Choice of treatment of T2D in youth should consider the greater insulin secretion burden in this population. Treatment options include metformin, sulfonylureas, thiazolidinediones, and GLP-1 agonists. Phase 3 trials in youth are in progress or recently finished for DPP-4 inhibitors, SGLT2 inhibitors and colesevelam. Other options for pediatric T1D therapy include bromocriptine, meglitinides and alpha-glucosidase inhibitors.

Adipose tissue insulin resistance constitutes a major pathophysiologic component of T2D. Adipose tissue has distinct morphologic features (white, brown, beige) and functions (energy storage, hormones secretion, energy balance, fatty acids metabolism, thermogenesis, and inflammation modulation). Cross-sectional studies in youth show that adipose tissue insulin resistance is higher in those with more severe obesity and the spectrum of abnormal glucose tolerance. Youth living with obesity who have impaired glucose tolerance (IGT) present altered suppression of lipid oxidation during the hyperinsulinemic-euglycemic clamp, and a lower disposition index relative to adipose tissue insulin resistance, than those with normal glucose tolerance. An adipose tissue insulin resistance index, calculated as the product of fasting insulin and fasting free fatty acids, is a predictor of IGT and T2D development in youth.

SYMPOSIUM 8: CGM

As the accuracy of CGM and flash glucose monitoring systems improves, use continues to increase. Time in range (70–180 mg/dl or 3.9–10 mmol/L) has been correlated to the development of diabetes complications using data from the Diabetes Control and Complications Trial and is being increasingly used as a primary outcome in the research setting as analysis. Twelve to 15 days of CGM data is considered adequate to predict the 3-month mean glucose level conveyed by an A1c. Including additional hours of CGM data increases the strength of the correlation with A1c.

Unlike fingerstick monitoring, which measures glucose levels in the blood, CGM systems measure interstitial glucose levels. When blood glucose is rising rapidly rising or falling, this creates a lag in establishing glucose equilibrium between the blood and interstitial tissue that results in a noticeable difference between the two measurements. Understanding this lag time is important for managing glycemia. Patients should be educated about the concept of lag time and should also be taught to consider CGM trend arrows when making diabetes treatment decisions.

The burden and fear of hypoglycemia is being increasingly recognized as a key factor limiting optimal glycemic control. CGM use has been shown to improve glycemic control and reduce hypoglycemia in people using both multiple daily injections and insulin pump therapy for T1D management. Although initially excluded from trials, recent studies have included individuals prone to hypoglycemia and have shown similar benefits in reduction of hypoglycemia. Individuals with and without impaired hypoglycemia awareness also benefit from the use of predictive low glucose suspend algorithms that use CGM glucose values to decrease or suspend insulin pump delivery in an effort to prevent or decrease the severity of hypoglycemia. However, healthcare professionals must carefully consider the potential concerns that device use may raise in children, including embarrassment from the device and alarms, increasing fear of hypoglycemia, and disruption of daily activities. Appropriate education about the optimal use of these devices is key to these improvements.

SYMPOSIUM 9: DIABETES IN THE DEVELOPING WORLD

There is a global epidemic of T1D and T2D in youth and the incidence is increasing. There are both moral and Human Rights obligations to provide diabetes care for all people with diabetes, however there are major disparities in access to care and outcomes between advantaged and less advantaged regions. Diabetes care requires community

awareness to make the diagnosis, access to well-trained, knowledgeable clinical teams, blood glucose monitoring systems, access to glucose control medications and injection devices, and non-glucose related treatments proven to prevent or retard diabetes complications. Collaborations between governmental and international societies and local non-governmental organizations are critical for establishing and sustaining pediatric diabetes centers of excellence in the developing world. These centers have been successfully utilized in India and Sudan to facilitate not only better care for patients, but also a better understanding of the epidemiology of diabetes in youth, disparities in diabetes care between advantaged and less advantaged regions, and potential solutions.

SYMPOSIUM 10: DIABETES ETIOLOGY

Advances in DNA sequencing have allowed for the identification of genetic variations among people with diabetes. Better understanding these endotypes will enable the development of individualized, targeted treatments for diabetes. For example, the *KCNJ11* variant in patients with maturity onset diabetes of the young (MODY) alters the K_{ATP} channels regulation in β-cells. Because sulfonylureas act on this channel, they are effective in patients with *KCNJ11* MODY. Other variants have a functional gradient from low to high risk of diabetes, such as the *HNF1A* variant. This variant can manifest in common alleles, when associated with T2D, population specific alleles, hypomorphic rare alleles and fully penetrant rare alleles, such as in the case of MODY. Relating to T2D, 450 variants on 300 loci have been associated with T2D risk. Knowledge on these variants is useful for target validation and patient stratification and to elaborate genetic risks scores of developing diabetes. As an example, PAM enzyme risk allele carriers exhibit incretin resistance, such that GLP-1 agonists may be less effective among these individuals.

Developmental origins may play an important role on Type 1 diabetes etiology. The increasing incidence of T1D over the last decade suggests that environmental factors are impacting genetic risk through what is referred to as gene–environment interactions. Children of a parent with T1D, of a higher birth weight, and a greater weight Z-score and rate of weight gain during infancy are at greater risk of developing islet autoimmunity, which peaks in the first few years of life. The mother's microbiome during pregnancy might also play a role, where mother with T1D present with more pro-inflammatory species and less short chain fatty acid-producing species. Other developmental environmental factors include the maternal and early life gut virome, as well as viral infections and vaccines received during childhood.

SYMPOSIUM 11: DIVERSITY AND INCLUSION

We all have biases. There are two groups of people when it comes to bias: those who acknowledge their bias and those who do not. Today's racism manifests differently than the overt acts of aggression from decades ago, through unconscious processes and micro-incivilities, or the daily behaviors such that signal to out-groups that they do not belong and are not welcome. In the work place, minority groups are more likely to be ignored and interrupted in conversation, are constantly scrutinized, and receive less eye contact than their majority peers. Black patients cared for by white doctors feel disrespected, less confident, less satisfied, and engage less and ask fewer questions of their white doctors. Based on these data, it is not surprising that black patients cared for by black doctors have better health related outcomes than black patients cared for by white doctors. In order to address our biases, we must question ourselves and our behaviors, collect and analyze data addressing these biases, create accountability for our actions, and provide training about bias and mitigating these tendencies. In taking these actions, we can pave a path for a more equitable, inclusive future in diabetes care.

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