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WILEY ISPAD

ANNOUNCEMENT

ISPAD Annual Conference 2018 Highlights

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The 44th annual ISPAD meeting took place from 11th to 14th October 2018 in Hyderabad India. The roving reporters present an overview of the scientific highlights of the meeting. Please also see the ISPAD Conference Resource Platform (http://medialibrary.ispad.cyim.com/) for online content including abstracts and video presentations.

1 | THE EMERGING DIGITAL WORLD OF DIABETES

Managing diabetes is complex and the burden of diabetes, even with new technologies, can be overwhelming. The diabetes digital world includes use of bio-sensors; various smart phone applications that advise on different aspects of diabetes care; social media platforms; and various diabetes platforms for downloading meters, insulin pumps and continuous glucose monitoring (CGM) device. These diabetes platforms allow remote monitoring by clinicians. Clinicians have to deal with big data of high velocity and volume. Data interpretation of downloads are complex and time consuming. A decision support system which helps with interpretation of downloads has recently been granted FDA approval. Decision support systems, automated insulin delivery and personal digital solutions represent a new evolution in management of patients with diabetes.

2 | PLENARY: REACHING THE UNREACHED

In 1993, ISPAD released the declaration of Kos with the intent to describe best care for children with Type 1 diabetes (T1D). However, children in many low resource countries are not receiving adequate care. In Mozambique, the average life expectancy following the diagnosis of diabetes is in many cases less than 1 year due to limited access to insulin and its high costs. In India, care of a child with diabetes can be as much as 1/5th of a family's total income.

In many limited resource areas, patients with T1D do not have access to a full care team. More change needs to happen by working with organizations such as the United Nations, Life for a Child, Changing Diabetes in children, and other worldwide organizations.

3 | SYMPOSIUM: NUTRITION

3.1 | Managing fat & protein

Fat and protein cause a delayed, sustained rise in glucose levels about 180-300 minutes after the meal. Traditional carbohydrate counting alone is insufficient to manage glucose levels with meals that contain either high fat or high protein content. However, adding additional insulin dosing ratios for protein and fat in addition to carbohydrate

ratios may add too much complexity to meal time dosing. Therefore, the speaker recommends increasing the pre-meal bolus (based on an insulin: carbohydrate ratio) by 15-20% when consuming a high protein/high fat meal (defined as at least 20 g fat or 30g protein) and extending the bolus delivery over 2-3 hours with 60% of the dose given before the meal. There is a lot of individual variability in insulin needs with protein/fat, therefore a 20% increase in dose is a conservative starting point and greater increases in dose may be needed to prevent delayed hyperglycemia.

3.2 | Fasting during Ramadan

Ramadan is an important holiday in the Muslim faith that involves fasting from dawn to dusk for a period of 30 days. During the fasting periods, food and drink is prohibited. Although being 'sick' is a permitted exception to fasting during Ramadan, many children with T1D and their families desire the child to participate in the fast. Children with T1D can fast if they are otherwise healthy, have stable glucose control and are 'hypoglycemic aware'. They should have a pre-Ramadan medical assessment with their provider and extensive education that includes an individualized diabetes management plan in preparation for fasting. Frequent blood glucose monitoring is essential to ensuring safety during fasting. Children should break the fast if they experience hypoglycemia, pronounced hyperglycemia, or acute illness.

4 | SYMPOSIUM: TECHNOLOGY TODAY

Individuals with T1D have lower life expectancy compared to the general population. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study confirm that poor glycemic control is associated with long term complications. It is not just Hemoglobin A1c (HbA1c) that affects morbidity and mortality, but also glucose variability. Technology offers the opportunity to decrease glucose variability, increase time in range (TIR), decrease time in hypoglycemia and time in hyperglycemia. For the same level of HbA1c, use of insulin pump therapy is associated with lower cardiovascular mortality, lower rates of retinopathy, peripheral nerve complications and diabetic keto-acidosis (DKA) than treatment with multiple daily insulin injections. CGM use is associated with an increase in the TIR and a decrease in the incidence of hypoglycemia. The Reimbursement Study of Continuous Glucose Monitoring (RESCUE Trial) in Belgium showed that use of CGM was cost effective leading to a reduction in hospital admissions and a nationwide saving of 345,508 Euros during the trial period.

5 | PLENARY: CLOSING THE LOOP

A closed loop system consists of a CGM that measures glucose levels, an algorithm that calculates insulin dosing based on CGM glucose values and an insulin pump that delivers insulin. Current closed loop systems are hybrid closed loop which requires carbohydrate counting or meal announcements. They can either be single hormone (insulin only) or dual hormone (insulin plus glucagon). Meta analyses show an increase in time in range and decrease time in hypoglycemia. These studies are limited since closed loop studies often include a small sample size with patients who are already in fair control. Studies have not been conducted in those with poor control. The Medtronic 670G was the first commercial closed loop system. Other systems are currently undergoing clinical trials. There is a community driven movement to develop closed loop systems via OpenAPS. Performance of closed loop systems can improve with increasing accuracy and reliability of CGM, developing faster insulins, and using alternative routes for insulin delivery, such as intra-peritoneal insulin delivery. Incorporation of adjunctive therapies (Glucagon-like peptide-1 (GLP-1) receptor agonists and pramlintide) may limit post-prandial hyperglycemia. Components of closed loop systems, such as interface, single device platforms, mobile or cloud connectivity and simplified user experience can all improve adherence. Future innovations include an improved big data strategy. The real future is in the biologic artificial pancreas that is bio-responsive. Clinical trials are beginning for islet cell encapsulation.

6 | SYMPOSIUM: INTERVENTIONS

6.1 | Insulin intervention strategies and prediction

In children with multiple islet autoantibodies, hyperglycemia is expected to develop in 50% within 6 years and in >80% within 12 years. By the time T1D manifests with symptomatic hyperglycemia, more than 80% of beta cell mass is already lost. The ongoing question is whether it is possible to start treatment of T1D at Stage 1 when patient is asymptomatic but has 2 or more autoantibodies? There are currently a number of programs where very young children are screened for presence of autoantibodies. In Fr1da insulin study, the aim is to study if it is possible to protect against further development progression to T1D by inducing immunological tolerance to beta cells by the administration of oral insulin in multiple islet autoantibody-positive children, while the aim of POInT (Primary Oral Insulin Trial) is to prevent the onset of T1D through the daily administration of oral insulin in children with a high risk of T1D. A benefit of participating in a screening program includes reduction in rates of DKA: A significantly lower prevalence of DKA at diabetes onset compared with population-based incidence studies has been reported in children who participated in 'The Environmental Determinants of Diabetes in the Young' (TEDDY) study probably due to knowledge of their genetic risks and close follow up for development of islet autoantibodies.

6.2 | Immunomodulation

Beta cell destruction is not linear and diabetes likely evolves in a relapsing-remitting fashion though beta cell loss is more abrupt during onset of illness. Insulitis is not always present in the pre-diabetes phase suggesting that non- immune processes may also contribute to development of diabetes. Pancreas sections from donors who were autoantibody-positive showed that insulin area and beta cell mass are maintained before disease onset whilst production of proinsulin

increases suggesting a processing defect in the conversion of proinsulin to insulin. Other non- immune processes include a genetic or post-translational defect of indoleamine 2 3-dioxygenase 1(IDO1). IDO1 is mainly expressed by beta cells in islets and attenuates autoimmunity in animal models. Loss of IDO1 enzyme precedes loss of beta cells in T1D patients.

Upregulation of Major Histocompatibility complex (MHC) Class I is a hall mark of T1D and is accompanied by infiltration of the islet cells by auto reactive and virus specific CD8 positive T cells. Autoreactive cytotoxic CD8 positive T lymphocytes are the main mediators of beta-cell destruction. Immune mediators postulated in T1D pathogenesis include interleukin 6 (IL-6) which is a pleotropic cytokine. Drugs that block IL-6 receptor (tocilizumab) has been successful in treating other autoimmune diseases e.g. juvenile arthritis. Phase 2 clinical trial of Tocilizumab in T1D is ongoing. It has been difficult to develop immunotherapy or prevention strategy for T1D because multiple factors appear to be involved in its pathogenesis, therefore, a combination therapy approach strategy may be needed.

7 | PLENARY: REACHING THE DISADVANTAGED

India is home to 20% of the world's population of children with T1D but only has few pediatric endocrinologists. Factors that can affect differences in clinical outcomes include differences in formal education, distance from basic health care, access to a diabetes team, knowledge of diabetes, family structure, individual psychological background, social stigma, and the family's economic situation. A registry study in Sweden showed that being born in Sweden increases risk of T1D in children who have origins in low-incidence countries. Despite this higher risk of diabetes in migrants, treatment is often less intense. Data from both India and Sweden suggest that a multidisciplinary and culturally sensitive approach is necessary to improve outcomes in children.

8 | SYMPOSIUM: INTERNATIONAL DIABETES FEDERATION (IDF)

The DCCT/ EDICT trials have shown that good glycemic control dramatically reduced complications. The DCCT adolescent was associated with increased risk of hypoglycemia but the strongest predictor for future severe hypoglycemia is a history of prior hypoglycemia. Pump use was associated with reduced risk of severe hypoglycemia. Other insight from the DCCT/ EDIC study include the finding that youth with T1D are unlikely to develop retinopathy before the age of 18 years if their initial screening showed no diabetes retinopathy. This finding offers opportunity to revisit screening guidelines.

Besides HbA1c there are other factors that need to be monitored in young people with T1D in order to maintain health and quality of life. These include blood pressure (BP), lipid profiles, financial and social factors etc. There are significant costs from having T1D and this means that a family's resources may be dramatically impacted. This can drive the family further into poverty, so divorce and desertion are common. Social issues such as stigmatization can impair the individuals function in school, work, family and society. Psychological illnesses such as depression can dramatically impact quality of life.

9 | SYMPOSIUM: EPIDEMIOLOGY

The incidence of diabetes in youth is increasing worldwide by ~2-5% each year. A majority of these cases are due to T1D with the greatest increase in incidence occurring in young children. The incidence of Type 2 diabetes (T2D) is also increasing sharply. 35% of all youth with diabetes live in USA, India and Brazil due to the large populations in those countries. 25% of patients in an Indian registry consisting of 9 urban clinics had T2D. In the SEARCH for Diabetes in Youth (SEARCH) surveillance system in the United States, the rate of T2D is increasing by 5% per year with the largest increase in minority youth. Youth with T2D have a greater risk of microvascular complications than those with T1D.

10 | SYMPOSIUM: UNDER TO OVER NUTRITION

Retrospective cohort studies in India have observed that coronary artery disease was more common in adults who were low birth weight (LBW) babies. It suggests that this may represent an example of programming which has led to persistent alterations in the structure and function of the developing organ in response to environmental factors. The SEARCH study is a prospective cohort study which has measured the prevalence, annual incidence and trends by age, race/ethnicity, sex, and diabetes type. It has shown that 1in 3 youth/ young adults with diabetes have at least 1 complication. The SEARCH ancillary nutrition study has shown a positive association between total carbohydrate intake, eating frequency and diabetes but no association between HbA1c and Vitamin D, breast feeding, age of introduction of complimentary feeds. The Australian Aboriginal cohort study set about to investigate whether the high rates of non-communicable disease seen in aboriginal patients was the result of processes that began in utero and continues after birth ('developmental origin of health and disease hypothesis'). Results to date show high rates of smoking, dual burden of overweight and underweight in the cohort. At 11, 18 and 25 years, participants who were LBW at birth remained smaller and lighter compared with those not LBW. Current weight and not birthweight was the predominant determinant of biomarkers of chronic disease in this cohort. This is thought to be the explanation for the low rates of diabetes in this cohort although the study participants are from a high-risk population.

11 | SYMPOSIUM COMPLICATIONS AND CO-MORBIDITIES

Digital retinal photography and computerized assessment of the retinal vasculature help us understand the effect of diabetes on retinal

blood vessels which may explain development of vascular complications. Retinal vessel diameter is associated with cardiovascular disease (CVD) with narrower arteriolar caliber changes being independently associated with an increased risk of CVD in women with T1D. Retinal arteriolar dilatation predicts retinopathy development in young patients with T1D. Greater retinal arteriolar tortuosity is associated with retinopathy and microalbuminuria.

The Adolescent Type 1 Diabetes Cardio-renal Intervention Trial (AdDIT) trial showed that use of an angiotensin-converting–enzyme (ACE) inhibitor and a statin had no impact on albumin: creatinine ratio. However, use of ACE inhibitor was associated with reduction in the cumulative incidence of microalbuminuria whilst use of stains was associated with lower levels of total cholesterol, LDL, and non-HDL cholesterol, triglycerides.

12 | SYMPOSIUM: ACUTE COMPLICATIONS

12.1 | Hypoglycemia and brain development

Hypoglycemia is a common complication in youth with diabetes and is a barrier to optimal control. The incidence of severe hypoglycemia has been decreasing over the years, due to advances in management and technology. The implications of hypoglycemia in diabetes are significant, with 6-10% of deaths in T1D due to hypoglycemia, many of which are driving accidents (though there is no data on the impact of hypoglycemia on others). It is important to note that no study has found clinically significant cognitive dysfunction in children with T1D overall. There have been trends found in decreased IQ and some deficits in executive function, so, larger differences may emerge with further research. Hypoglycemia is associated with decreased verbal and IQ scores, with greater frequency of hypoglycemia associated with worse performance on attention tasks and cognitive function. However, changes are subtle, and it is questionable if hypoglycemia affects academic achievement (of note, hyperglycemia may have more of an effect on achievement than hypoglycemia).

12.2 | Effect of hyperglycemia on the brain

Studies have shown that acute hyperglycemia leads to changes in cognitive function. For every 5% increase in time in hyperglycemia, scores on cognitive function tests decreased, though this relationship may be a U-shaped curve. Pittsburgh Epidemiology of Diabetes Complications Study showed that clinically relevant cognitive impairment was five times higher in adults with T1D compared to other adults, and the impairment was worse if HbA1c was >7.5% (58mmol/mol) or microvascular disease was present. In the Medalists cohort, cognitive function deficits were found, including delayed recall and decreased psychomotor speed. In the Royal Children's Hospital (RCH) cohort study, with 12 years of follow-up, children with T1D had decreased IQ performance and change in brain morphology. In their early twenties, it was observed that T2 signals and volumes decreased with age – a sign of "accelerated" aging. This is thought to be because glucose is fuel for the brain and T1D is an exemplar of disordered homeostasis. In summary, hyperglycemia is just as significant as hypoglycemia in terms of impact on cognitive function.

12.3 | Subcutaneous insulin in DKA

The goals of DKA treatment are to correct dehydration and replace electrolytes, arrest ketogenesis and correct acidemia, and restore glucose to near normal levels.

Studies in adults comparing use of low-dose insulin for DKA given by intravenous route (IV), subcutaneous injection, or intramuscular injection showed that ketones and glucose levels decreased to the same extent within 8 hours, regardless of route of administration, suggesting that the route is not critical. In children, intravenous administration of regular insulin was compared to subcutaneous lispro insulin. The results showed that while acidosis took longer to resolve after glucose levels reached 250 mg/dL, all recovered from DKA without complications suggesting that subcutaneous administration could be a cost-effective alternative for DKA management especially in low resource countries.

13 | SYMPOSIUM: ISPAD GUIDELINES RELEASE

ISPAD released new guidelines in 2018, which updates the previous guidelines from 2014. Each chapter includes sections for three levels of care: recommended, comprehensive, and limited care. Evidence-based grading was used for clinical practice recommendations. Three new chapters were added in 2018, including a chapter on the use of technology in diabetes, guidelines for children while attending school, and management of diabetes in toddler or preschool aged children.

The 2018 guidelines present new recommendations regarding glycemic control targets for children with T1D. An individualized target of glycemic control is recommended for patients younger than 25 years. An HbA1c of <7% (53 mmol/mol) was set as a target for those children receiving comprehensive or recommended care. The lower target was influenced by knowledge of the deleterious effect of hyperglycemia on cognitive function and the fact that use of technology and new insulin delivery methods have decreased the risk of severe hypoglycemia. A target HbA1c of <7.5% (58 mmol/mol) may be acceptable if the child has the inability to articulate symptoms of hypoglycemia, has hypoglycemic unawareness, or is in a resource-limited setting. A target HbA1c of 6.5% (47.5 mmol/mol) is appropriate for a child still in the honeymoon period and no significant hypoglycemia is observed. The recommended target HbA1c for youth with T2D is <7%, and the overall recommendation is to intensify treatment as fast as required.

14 | PLENARY: NEWER TREATMENTS

Faster acting insulins are required to decrease postprandial hyperglycemia. Inhaled insulin is absorbed quickly but requires good respiratory function. Newer basal insulins aim to increase the duration of

action and decrease insulin level variability. Smart insulins that release insulin when glucose levels rise is experimental. Nasal glucagon has been shown to be as effective as intramuscular glucagon. In T2D lifestyle modifications and medications are usually required to meet glycemic targets. Metformin is first line therapy but there is often a progressive decline in control in the first year. Once the HbA1c reaches 7%, second line therapies should be started. Insulin therapy should be initiated once the HbA1c reaches 9%. Newer agents including Glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones and Sodium-glucose co-transporter-2 (SGLT2) inhibitors hold promise; however, further research is required to define their role in pediatrics. Bariatric surgery in T2D adolescents improves HbA1c, blood pressure, lipids, obstructive sleep apnea, polycystic ovary syndrome and fatty liver though adverse events following surgery need to be considered.

15 | SYMPOSIUM: COMMUNICATION

Empathy and patience are essential for education of children and their families. Patients and families may have health illiteracy or illiteracy. Health illiteracy and low literacy can be barriers to diabetes education. However, various tools are available to facilitate education such as educational toys, pictorial maps, audiovisual stories, skits, games and fun activities. With the increase in the use of social media worldwide, patients and families may be able to find empathy from others with T1D. Social media can also increase awareness for a cause, promote participation, increase fundraising and increase involvement. However, social media can be detrimental as it might create misconception, shame, and bullying.

There is a need to strike a balance between privacy and informatics so that epidemiology and research are enriched while people maintain privacy as a fundamental right.

16 | PLENARY: MENTAL HEALTH PROFESSIONALS ARE A MUST ON EVERY TEAM

Treatment of T1D is very demanding and can have an emotional burden resulting in only 21% of adolescents achieving glycemic targets. One method of assessing the emotional burden of T1D is to measure health related quality of life (HRQOL), which is an individual's subjective experience of illness and the impact that illness and its treatment has on the individual's functioning across a variety of domains. HRQOL can be assessed from the patient's perspective as well as the parents' perspective. The larger the difference between the child's HRQOL and the parent's perception, the higher the HbA1c. The HVIDORE study, SEARCH study, TEENs study have all looked at HRQOL in pediatrics. Female gender, higher HbA1c, lower exercise levels, and unhealthier eating habits are associated with lower HRQOL. Successful behavioral interventions are multicomponent and include diabetes skills, problem solving, coping skills, and setting realistic expectations of both the youth and the parent. These interventions should be integrated into routine diabetes care. It is important to encourage autonomy while encouraging parental support.

17 | SYMPOSIUM: REGISTRIES

The SWEET Project was started in Europe with the aim to create centers of reference for high standard of care and harmonize care for all children and adolescents with diabetes mellitus across the world. SWEET Project creates opportunities to improve diabetes care as we learn from each other, share knowledge, skills and experience. The culture of open benchmarking helps to improve patient care.