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ISPAD GUIDELINES

ISPAD Annual Conference 2022 highlights

Sze May Ng[1,2,3] | Helen Day[1] | Jody B. Grundman[4] | Peerzada Ovais Ahmad[5] | Maja Raicevic[6] | Tinotenda Dzikiti[7] | Nancy Katkat[8] | Anju Jacob[9] | Marisa Ferreira Clemente[10] | Hussain Alsaffar[11,12] | Yasmine Ibrahim Elhenawy[13] | Yasmine Abdelmeguid[14] | Klemen Dovc[15]

[1]Paediatric Department, Southport and Ormskirk NHS Trust, Ormskirk, UK

[2]Faculty of Health, Social Care & Medicine, Edge Hill University, UK

[3]Department of Women's and Children's Health, University of Liverpool, Liverpool, UK

[4]Children's National Hospital, Washington, DC, USA

[5]Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India

[6]Institute for Children's Diseases, Clinical Centre of Montenegro, Podgorica, Montenegro

[7]#dedoc and Zimbabwe Diabetes Association, Harare, Zimbabwe

[8]Paediatric Department, Blackpool Teaching Hospital, UK

[9]Al Jalila Childrens Specialty Hospital, Dubai, UAE

[10]Department of Paediatric Diabetes, Alder Hey Children's Hospital, UK

[11]Child Health Department, Pediatric Endocrine and Diabetes Unit, Sultan Qaboos University Hospital, Muscat, Oman

[12]College of Medicine, Wasit University, Wasit, Iraq

[13]Pediatric and Adolescent Diabetes Unit, Faculty of Medicine, Ain Shams University, Cairo, Egypt

[14]Pediatrics Endocrinology and Diabetology, Alexandria University, Egypt

[15]Department of Pediatric Endocrinology, Diabetes and Metabolic Diseases, UMC – University Children's Hospital, and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Correspondence
Sze May Ng, Paediatric Department, Southport and Ormskirk NHS Trust, Ormskirk L39 2AZ, UK.
Email: may.ng@nhs.net

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1 | PLENARY—ADVANCES IN DIABETES TREATMENT

Clinical trials performed in the last three decades have shown that restoration of beta-cell function via transplantation of isolated islet cells allowed the achievement of a more physiological release of endocrine hormones. The future of insulin-producing cells is expected to progress to implantation without requiring immunosuppression by using gene editing, allowing the production of immune-evasive cells. Viral infections have long been considered possible candidates for environmental triggers in genetically susceptible individuals with type 1 diabetes (T1D). Epidemiological studies have demonstrated that enterovirus infections are associated with the development of islet autoimmunity and T1D. The Diabetes Virus Detection (DiViD) study reported the presence of enterovirus genome by a polymerase chain reaction and of enterovirus proteins by immunohistochemistry in pancreatic sections. The evidence from the DiViD study could provide evidence that an enterovirus vaccine may potentially be effective for the primary and secondary prevention of T1D. A prospective, randomized controlled DiVid interventional study is now in progress, using antiviral treatment (pleconaril and ribavirin) for 6 months in newly diagnosed individuals with T1D. Novel immunotherapies for different T1D endotypes are currently underway, using bionics, chimeric antigen receptor (CAR)-engineered regulatory T cells (Tregs) and vaccination with tolerogenic dendritic cells. Currently, five immunotherapies have been shown to preserve insulin secretion in patients with newly diagnosed T1D: teplizumab, otelixizumab, rituximab, abatacept, low-dose anti-thymocyte globulin and alefacept, most of them having an acceptable safety profile and side effect. The expected approval

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of teplizumab by the FDA and EMA will force the treatment paradigm of T1D to shift by placing a greater emphasis on screening for T1D and by driving the market revolving around individuals with T1D toward precision medicine.

2 | SYMPOSIUM—NUTRITION MANAGEMENT IN DIABETES

Continuous glucose monitoring (CGM) has become a routine part of clinical practice as it provides glucose metrics that healthcare professionals can analyze with families and provide valuable information regarding glucose control, moving from HbA1c outcomes to CGM metrics outcomes. Some of the key features to discuss with the families about CGM metrics include time in range, time above and below range and the visualization of the graphs allowing them to have a better comprehension of the impact of nutrition choices on glucose behavior. Families reported that CGM had increased their awareness of the different impacts of foods and snacks. The prevalence of celiac disease in T1D ranges from 1 to 16% worldwide. The greatest risk is associated with children diagnosed with T1D before 5 years of age and with longer diabetes duration. ISPAD and ADA recommend screening for celiac disease should be performed soon after diagnosis of T1D, and at 2 to 5 years intervals (sooner if symptomatic or having a first-degree relative with celiac disease). Literature indicates that the normalization time of celiac titers depends on the degree of serology elevation and severity of intestinal damage. In practice, it might take as long as 4 years, despite a strict gluten-free diet. Long-standing celiac disease in individuals with T1D increases the risk of retinopathy and nephropathy, higher bone fracture risk and higher rates of concomitant autoimmune thyroid disease. These individuals are at greater risk for depression and eating disorders.

3 | SYMPOSIUM—REGISTRIES: WHY ARE THEY IMPORTANT?

Registries are a systematic and organized way of data collection that helps in evaluating specific outcomes, as well as contributing to quality improvement, surveillance, and benchmarking. Registries play an important role in improving patients' care and serve as a reliable guide for health authorities, insurance companies and other health organizations. Collaborative comparisons between international pediatric diabetes registries and the blending of their data may pave the way for the development of more relevant international guidelines. There are multiple T1D registries globally. In 2016, the T1D Exchange Quality Improvement Collaborative (T1DX-QI) registry, included data from more than 50 centers in the United States of America. The Kuwaiti experience CODeR (Childhood Onset Diabetes Electronic Registry) was also developed in the Middle East. Registries are important tools and provide an important source of information that could help in monitoring the progression of the disease and the course of its complication, identify risk factors, estimate costs and direct resources, design prevention programs, and improve the standard of care locally and globally.

4 | PLENARY—DIGITALIZATION IN DIABETES EDUCATION AND CARE

The advances in diabetes technology have identified health inequalities within areas such as deprivation and ethnicity. Healthcare professionals are challenged to integrate technology and digitalization of diabetes education and care into routine diabetes management, but ensuring that underserved populations do not miss out is a key priority. "Big Data" collection helps to identify metabolic models for staging T1D and to identify therapeutic outcomes. It also allows healthcare professionals to identify individual outcomes and support those living with diabetes. "Voice bio marker identification" is being currently researched to identify vocal biomarkers for screening diabetes and monitoring the health of those living with the condition. The "Colive Voice Study" have recognized that those living with diabetes have distinct vocal signatures compared to the general population. The study aims to look at this research data being integrated into artificial intelligence delivery algorithms, using vocal assistance to support patient management and monitoring in the future.

5 | SYMPOSIUM—MENTAL HEALTH IN DIABETES

Diabetes burnout may be a result of the relentless daily tasks of living with T1D. Health professionals must recognize the difference between distress and depression. Depression is a psychiatric condition that is more than burnout or distress, and the symptoms interfere with day-to-day functions. Distress in teenagers is linked to worsening self-care behaviors and sub-optimal glycemic management. Diabetes distress is recognized to be higher within lower social economic groups and those with racial and ethnic minority backgrounds. However, teenagers with strong peer support have shown that they are less likely to experience diabetes distress. The statistics show that the prevalence of a clinically diagnosed eating disorder is greater in women with Type 1 diabetes and this is twice greater in adolescents with T1D. The physical and psychological impact of an eating disorder increases the risk of diabetic ketoacidosis, long-term complications associated with diabetes and strong negative emotions resulting in increased depression and suicidal thoughts. As health professionals, it is important to develop knowledge about eating disorders in those living with diabetes and to establish appropriate treatment pathways.

6 | SYMPOSIUM—UPDATES ON COVID AND DIABETES IN CHILDREN

During the COVID-19 pandemic, new approaches in clinical follow-up were developed using telemedicine consultations and remote educational sessions. Studies focusing on the doctor-patient relationship in synchronous real-time video consultations compared to in-person visits concluded that patient-care satisfaction and perception of the doctor-patient relationship, along with patients' perception of

physician empathy did not substantially differ between the two forms of consultation. Adults with T1D registered worsening of metabolic control associated with a significant reduction of physical activity during lockdown due to COVID-19 pandemic, which disagreed with data from pediatric participants. This difference may relate to the normal activity in children that can compensate for the lack of structured physical exercise. CoVidentary, an innovative online exercise training program created during the pandemic in Italy used social media to reduce sedentary behaviors in children with T1D during the pandemic and a virtual camp to monitor glycemic management. Exercise and nutrition advice and management were some of the initiatives developed to compensate lockdown restrictions and improve glycemic management.

7 | JOINT SYMPOSIUM—JDRF-ISPAD: ACCESS TO CARE CHALLENGES AND SOLUTIONS

The challenges of living with T1D are greater in low-middle-income countries (LMICs). These include limited health coverage for insulin, skilled multidisciplinary teams, and comprehensive diabetes education programs. Something unique to developing countries is that there is a large out-of-pocket expense that puts a disproportional burden for healthcare on those in low-income households. There are also issues related to the public health system which is overburdened and commonly provides varying standards of care in primary or tertiary settings, with a lack of regular follow-up or established registry to adequately track outcome data. Barriers to access to insulin in LMICs are related to regulation, production costs and complex regulatory assessment. Prescription issues include a lack of clinical guidelines, a lack of sustainable training for healthcare providers and a limited understanding of healthcare providers about biosimilars. Novel innovations in insulin and glucose testing need to meaningfully involve people with T1D and their caregivers from low-income settings Additional strategies to address challenges include removing barriers that hinder competition, ensuring that products on the market are quality assured by a regulatory authority, pooling procurement at the national level, ensuring price transparency in the supply chain and developing clinical guidelines within the health systems.

8 | SYMPOSIUM—PREDICTION AND PREVENTION OF TYPE 1 DIABETES

The vast majority of individuals that have two or more antibodies progress to T1D diagnosis. Progression differs by age, as those identified under the age of 9 progress faster, and those over the age of 20 progress more slowly. The concept of endotypes in T1D is based on the first autoantibody specificity and age at diagnosis (<7 years, 7–12 years, >12 years). Current investigations looking at the role of enterovirus in developing T1D found that IAA first endotype risk was associated with coxsackie B1, and no risk was seen with GADA. Primary prevention trials are currently investigating rituximab, teplizumab, abatacept, and autoantigen-specific therapy. Secondary prevention trials are investigating the use of anti-CD3, teplizumab, abatacept, hydroxychloroquine, golimumab, and liraglutide. Teplizumab treatment for 14 days was the first drug shown to be able to slow the disease process leading to T1D in high-risk individuals. Other developments have shown a rapid decline in gut microbiota diversity in those with T1D. Fecal transplantation can potentially improve diversity, rearrange gut metabolites with immunomodulatory effects, restore gut permeability, and incite changes in the immune system. In a study where individuals were randomized to receive stool from a healthy young donor or autologous feces from self, there was stabilization in fasting and stimulated c-peptide in both groups but not for all participants.

9 | PLENARY—OBESITY AND ITS MANAGEMENT

The prevalence of childhood obesity is increasing worldwide. Obesity in childhood is a multi-faceted disease with genetic, metabolic, environmental and behavioral factors that interact with each other. Greater severity of obesity is associated with a greater risk of low HDL cholesterol, high systolic and diastolic blood pressure, and high triglyceride and HbA1c. The ENDO Society recommends the use of drugs only after failure of lifestyle changes and pharmacotherapy options for children are limited. Orlistat reduces fat absorption by inhibiting pancreatic lipases but the safety/efficacy profile for children <12 years has not been established. Phentermine demonstrated enhanced weight loss in many, but there are several adverse events in adolescents, and it is currently only approved for >16 years. Liraglutide leads to a significantly greater reduction in BMI SD score with lifestyle changes compared to placebo, with greater improvements in BMI and body weight. Phentermine/topiramate offered statistically significant reductions in BMI and favorably impacted triglyceride and HDL-C levels in adolescents with obesity. The meta-analysis concluded that liraglutide had a higher probability of achieving clinically significant weight loss compared with other drugs, while topiramate was superior in safety. There are ongoing combination therapies being studied in adults and children that show combination therapy achieves higher weight loss, and patients prescribed >3 medications lost significantly more weight than those prescribed 2 or no anti-obesity medications at 12 months. Currently, the need to select therapy is based on affordability and insurance coverage. Bariatric surgery in adolescents have also demonstrated a higher likelihood of having remission of type 2 diabetes and hypertension compared to adults.

10 | SYMPOSIUM—UPDATES ON TECHNOLOGY IN DIABETES CARE

The iLet Bionic Pancreas could be the preferred option for patients with T1D in the future who want less interaction and a simpler

interface with the insulin delivery system as it requires no adjustments of basal rates and bolus settings, no carb counting or manual correction boluses, This investigational insulin delivery system is a closed loop system which uses a mono- (insulin) or bi- hormonal (insulin and glucagon) therapy. The glucose target is the only setting to adjust, and the device adapts continuously to the individual insulin needs and carbohydrate counting is not needed. In the pediatric cohort of 165 participants, HbA1c were 0.5% lower in patients with the bionic pancreas compared to those on standard care. Despite the increasing availability of licensed closed loops, open-source automated insulin delivery systems are still in the game. Arguments for open-source automated insulin delivery systems include technological advantages such as customizable personal profile, remote control of profile, unavailability of hybrid closed loop system in some countries, unachieved therapy goals and less frequent interaction with diabetes technology.

11 | JOINT SYMPOSIUM—ATTD-ISPAD: ADVANCED TECHNOLOGY IN DIABETES

Artificial intelligence is often used to describe machines that mimic human cognitive functions. Clinical Decision Support System (CDSS) provides clinicians, staff and individuals with knowledge and person-specific information to enhance their health care. A wide range of CDSS is available to cover all aspects of diabetes care and could be classified into the following groups: (1) tools for people with diabetes self-management (personalized nutrition support and physical activity), (2) screening and prevention for diabetes-related complications, (3) prediction tools for identification of people more likely to develop diabetes, and (4) clinical management support. The idea is to improve clinical outcomes, increase access to care, enhance the utilization of healthcare resources and provide precision medicine, allocating always the decision comparable to the one that an experienced physician would provide. Open-source automated insulin-delivery systems have been extensively studied, and are safe, effective and have the potential to help a wide population of individuals with T1D alongside commercial systems. Every healthcare professional is responsible to learn about all treatment options, including open-source systems while these systems should fully disclose how they operate to enable healthcare professionals and patients to understand the benefits and limits of these systems.

12 | JOINT SYMPOSIUM ASPED-ISPAD: DIABETES & FASTING

Fasting is a part of many religions, and the best example of this is Ramadan fasting. Advancing technology has made it possible to fast safely. The challenges of fasting with diabetes include the risk of hypoglycemia, hyperglycemia, ketoacidosis, dehydration and thrombosis. There are some exemptions from religious fasting such as very young age, women who are pregnant or breastfeeding, persons with intellectual disabilities and individuals who are travelling or doing heavy physical labor. If a person with T1D wishes to fast, a risk assessment is important. A New DaR-IDF Risk score is available to help in making this decision. Interventions should also be planned ahead to ensure safe fasting, and these include pre-fast counselling, pre-fast glycemic optimization, frequent blood glucose monitoring, insulin modifications, nutrition and activity. Blood glucose monitoring is an essential element to risk quantification for people wishing to fast. Pre-fasting nutritional education is crucial for safe fasting and an individualized dietary plan is needed to maintain a healthy body weight, avoid excessive weight changes and minimize complication risk. Necessary dietary modifications should be made such as type of food, time of meals, insulin regimen and ensuring knowledge about carbohydrate counting. Advancing technologies such as CGM have also made it possible to fast safely, as it provides an accurate and reliable understanding of blood glucose changes, duration of hyperglycemia as well as time in target.

13 | JOINT SYMPOSIUM ESPE-ISPAD: MONOGENIC AND OTHER FORMS OF DIABETES

Monogenic diabetes is a heterogenous condition, caused by one or more defects in a single gene or chromosomal locus. Combined, monogenic diabetes accounts for approximately 2.5%–6.5% of pediatric diabetes. The list of genes causing monogenic diabetes is growing fast (more than 50 genes have been identified so far, associated with either T-cell dysfunction (T1DB-like), insulin receptor defect (T2D-like), or monogenic autoimmunity) and this underscores the need for comprehensive next-generation sequencing (NGS) as the best diagnostic approach. Early and accurate diagnosis can guide treatment, rather than phenotype-based targeted testing, particularly for neonatal diabetes (NDM). Glibenclamide, which stimulates insulin release from pancreatic beta-cells by inhibiting ATP-sensitive potassium channels, could be used as a specific treatment of NDM due to KATP channel mutations. Glibenclamide is also a neuroprotective drug and has been shown to improve neurological features in NDM such as epilepsy, motor function, global neurological improvement, and hypotonia. Glibenclamide oral suspension (Amglidia) has been designed for premature, neonates, toddlers and children and is as efficient as tablets. Monogenic diabetes in Arab regions has a different spectrum and is mostly associated with a rare familial recessive syndrome. Neonatal diabetes is more common in Arabs and has a different genetic etiology compared to other populations, associated also with a higher rate of consanguinity. The most frequent etiology reported in this region is Wolcott-Rallison syndrome due to EIF2AK3 mutations. On the other hand, data on MODY in Arabs are limited, which might be due to unknown genetic mechanisms contributing to the pathogenesis of MODY in Arabs.

14 | SYMPOSIUM—IMPACT OF DIABETES ON BEHAVIOR

Sleep is vitally important in the early years of life, and it is fundamental for brain development. Humans spent a third of their lives asleep.

Out of six main categories of sleep disorders, diabetes mellitus contributes to two of them; "parasomnias" resulting from enuresis, and "sleep-related movement disorder," especially in people living with T1DM for a long time. Sleep disturbance could increase the vulnerability to some psychological disorders including depression. A chronic condition such as T1D that requires constant monitoring results in sleep disturbance due to several factors such as staying awake late to deal with hypoglycemia, waking during the night to correct for hyperglycemia, or struggling to fall asleep due to a late sweet snack. Sleep has to be kept high on the research agenda to learn how best to support families to find the balance between waking to manage diabetes and sleeping for health. Evidence-based intervention strategies include behavioral parent training in improving communication, encouraging behavior management, promoting structure within the family, and planning ahead. Digital interventions to improve self-care and mental health in young people such as the self-compassion chatbot "COMPASS" were found to be helpful in improving the well-being of adolescents living with T1DM. Future directions recommended include developing digital tools that incorporate evidence-based psychological theories, use of digital tools to augment face-to-face therapy, involving young people in the development and including parents and families in the delivery are needed.

15 | JOINT SYMPOSIUM ISPAE-ISPAD: DIABETES CARE SYSTEMS SET-UP

Task shifting and sharing involve the redistribution or delegation of healthcare tasks within the task workforce and communities. Task shifting occurs when a task is transferred or delegated while task sharing occurs when tasks are completed collaboratively between providers with different levels of training. The purpose of task sharing or shifting is to reduce morbidity, mortality and burden of the disease among the populations where a shortage or inaccessibility of highly skilled professional health workers limits access to effective care so that shifting or sharing achieves this purpose by positioning providers with less training to deliver effective interventions thereby improving access to and coverage of those interventions without compromising standards of care. In LMICs, patient access to multidisciplinary teams is limited. LFAC ISPAD-Task shifting survey reported on gaps in access to skilled medical, nursing and AHPs for young people with T1D in LMICs. The responsibility of T1D care in Uganda lies primarily at the primary healthcare centers and not at the tertiary hospitals. Care in Uganda is mainly provided by nurses working in isolated clinics with limited drugs and equipment. In Uganda, internet penetration is only about 26.2% of the total 47 million population, while only half the population has mobile phone connections. PEN-Plus is part of an ecosystem where care and treatment are provided at first-level district hospitals. Decentralizing of T1D care through the PEN-Plus was achieved by mid-level providers who are trained in T1D to facilitate follow-up and management of T1D.

16 | SYMPOSIUM—DIABETES PUBLICATIONS SPECIAL HIGHLIGHTS

Numerous studies were published in the last year describing clinical investigations of type 1 or type 2 diabetes care, including recent findings in the understanding of diabetes etiology and possible prevention strategies, novel (adjunctive) pharmacological molecules and state-of-the-art technological approaches. Based on a growing body of evidence that supports the technological advantages, the management of type 1 diabetes is changing substantially almost in real-time. Automated insulin delivery (AID) consists of a CGM that measures the glucose concentration, an insulin pump, and an algorithm that uses glucose concentration and prior insulin delivery data to control insulin delivery in a glucose-responsive manner is becoming the standard of care and is recommended for youth with diabetes were available in the latest ISPAD clinical guidelines. Recent randomized controlled trials have demonstrated the efficacy and safety of different control algorithms and have included different populations, including very young children with T1D and children with newly diagnosed T1D. These data were complemented with data from large multinational registries. Clinical outcomes in diabetes are unfortunately determined by disparities in socioeconomic status and consequently in inequities in diabetes care. Data from underserved countries and communities are critical in understanding barriers to technology use, including limited accessibility and reimbursement policies, and thus could help us develop targeted interventions to address these disparate outcomes.

17 | JOINT SYMPOSIUM IDF–ISPAD: HOW TO IMPROVE THE LONG-TERM DIABETES OUTCOME?

Life for a Child in collaboration with ISPAD, JDRF and IDF, has developed the T1D Index data simulation tool mapping the impact of T1D. The T1D index measures the human, public health, and economic impact of T1D throughout the world and at the country level. Incidence, prevalence and mortality are used to model estimates of new cases of T1D in a year by country, age group and risk of mortality and complications. There are approximately 9 million individuals estimated living with T1D globally. The global average for a person diagnosed with T1D at 10 years old will live 42 unburdened years but will have 32 healthy years lost due to early mortality, disability and complications. Timely diagnosis, access to insulin, test strips and new preventative therapies are strategies that could lead to 4 million fewer lives lost by 2040. Vascular complications and mortality rates remain a real challenge for young people with T1D requiring early prevention and detection for better outcomes. Data from the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) showed that subclinical increases in albumin creatinine ratio (ACR) may provide a valuable tool to identify adolescents at higher risk of vascular complications. The keys to preventing complications during adolescence include good glycemic management, lifestyle interventions, angiotensin-converting enzymes (ACE) inhibitors, statins, and psychological and motivational interventions.

AUTHOR CONTRIBUTIONS

All authors wrote the draft and approved the final manuscript.

CONFLICT OF INTEREST

All the authors declare no other conflict of interests.

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Not applicable.

ORCID

Sze May Ng https://orcid.org/0000-0002-3449-0541

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