Hormone Research in Paediatrics

Meeting Report

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ISPAD Annual Conference Highlights 2023

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Plenary – Prediction and Prevention of T1DM

Currently, the best available biomarkers for type 1 diabetes (T1D) prediction are autoantibodies, defined HLA haplotypes and genetic risk scores. Examples of important initiatives improving T1D prediction are DiaUnion (interregional screening study) and Danish National Birth Cohort (DNBC) screening program, a Sweden and Denmark population-based screening program. Both programs included a precision prediction approach including extended genetic risk score, Omic technologies for better understanding of beta-cell prediction profiles with the aid of machine learning and the use of artificial intelligence. Experience from DiaUnion and DNBC screening programs proved that precision prediction approaches including extended genetic risk score, lipidomic, metabolomics, proteomics, transcriptomics, methylation status as well as beta cell markers are crucial for improving the prediction of T1D. As there is a symbiotic relationship between gut

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microbes and our body, gut microbes are regarded as an essential modulator of T1D pathology. There are 445 trials with fecal microbiota transplantation going on worldwide. The Amsterdam GUTDM1 study found that fecal microbiota transplantation halts the decline in endogenous insulin production in recently diagnosed T1D.

Symposium – T1D Therapeutics New Approaches for an Old Disease

When designing preventive trials besides staging of T1D, it is important to consider factors such as age, genetic risk score and other non-genetic risk scores incorporating metabolic parameters. In primary prevention, the endpoint is the development of autoantibodies with most studies exploring the link between dietary prevention and associations. Secondary prevention trials focus on individuals with ≥2 autoantibodies; the endpoint in these trials is progression to stage 3 T1D. TrialNet TN10 study showed that teplizumab successfully delayed the onset of stage 3 by 2 years. Although different studies failed to slow T1D progression, they had positive immunologic-metabolic effects raising the possibility of combination therapy with drugs targeting different underlying factors in the development of T1D. Verapamil trial resulted in partially preserved stimulated C-peptide secretion at 52 weeks from diagnosis compared with placebo. T1D RELAY study is an example of combination/sequential therapy including both rituximab (anti-CD20) followed by abatacept (CTLA4-Ig) in newly diagnosed T1D. Recent innovative technologies including 3D Bioprinting, encapsulation, organ decellularisation and gene editing were important strategies to overcome obstacles with beta cell transplantation. Future direction lies therefore in a likely combination of preventive and immunotherapies.

Symposium – Care Models and Value-Based Healthcare

The paradigm of diabetes-related healthcare has changed rapidly throughout the last 30 years from task-oriented to technology-driven and might even evolve into a disease modification paradigm. Each of these paradigms poses different challenges and requires a different approach from healthcare providers. While the traditional, task-oriented paradigm generally leads to higher level of centralisation of care, the more recent technology-driven paradigm allows for a higher degree of autonomy in persons with diabetes. The main objective for clinics in low-income setting is to provide adequate care from all accessible areas. With that in mind, it is paramount to set the clinics in a place that is easily accessible. Last but not least, non-governmental partners should be secured to increase sustainability of the newly set programs and initiatives.

Symposium – Highlights of Diabetes Publications for 2022

Publications on the use of automated insulin delivery systems and continuous glucose monitoring (CGM) systems into real-world use has shown good outcomes. However, despite the current diabetes technology, many still do not meet glycaemic goals which highlight the need for adjunct medications and new insulins. Studies have shown promising results in antigen-specific immunotherapy, although limitations still exist where clearly responders and non-responders differ. Among SGLT inhibitors, sotagliflozin, a dual inhibitor has recently been approved in Europe for use in T1D in adults. Among new insulins, an ultra-long agonist (icodec) has moved to phase 3 trials. Further progress is being made with inhaled insulin (Afrezza) with very rapid time-to-peak and rapid offset as well as with future development of smart insulins. Studies continuously show that type 2 diabetes (T2D) is on the rise among children and T2D is often accompanied by obesity, hypertension, and hypertriglyceridemia even in children/adolescents. Treatment possibilities for obesity and T2D must be increased to include the paediatric populations.

Plenary – Health: Outcome and Value

The importance of value-based funding and governance in healthcare was emphasised and digital transformation in healthcare was a key area to evaluate behavioural changes and cultural shifts. Challenges related to data sharing and research costs in Africa were mentioned, and there was a call to transition away from fee-for-service models. Studies regarding incentivising healthcare professionals and challenges in identifying patient classifications highlighted the importance of data monitoring, patient engagement and cost identification as critical aspects of value healthcare integration. Trust and patient identification were key themes in healthcare projects. Significant cost savings and remote monitoring were highlighted with a focus on improving outcomes and reducing costs through collaboration and technology.

Symposium – Implementing Diabetes Care in Low-Middle-Income Countries

The introduction of a program to enhance diabetes care standards for physicians and patients in Egypt to strengthen diabetes care infrastructure, including a mentor program, educational hubs, mobile apps, and patient support projects was described. In India, similar initiatives were described such as bridge programs for junior paediatric endocrinologists and mentorship programmes for registered nurses, dietitians, and patient advocates with support from local organisations. Efforts are currently taking place to enhance diabetes care in India and Africa through education and multidisciplinary training. In many low-middle-income countries, there is a pressing need to enhance diabetes care infrastructure, management, education, and awareness in resource-constrained regions. Collaboration with governments, education and international support are essential for advancing healthcare standards and delivering improved care for individuals with diabetes in these countries.

Symposium – #DEDOC°: The Patient Voice at ISPAD

The importance of peer support and community diabetes advocacy was highlighted with patient experiences shared. There was a vital role of online communities in providing support, resources, and a sense of belonging for people with diabetes. Development of peer support programs was associated with a positive impact on diabetes management for people living with diabetes. The significance of prioritising the voices of people with diabetes, engaging with the community, developing guidelines, diabetes resources and addressing various issues like stigma and mental health were also discussed, emphasising the importance of ongoing conversations, research and community input into diabetes advocacy.

Symposium – How to Advocate for Psychology Services in Diabetes Centres

T1D is a demanding chronic condition where emotional health is crucial and psychological intervention is needed as distress from living with diabetes can occur at any time. Self-management and quality of life are affected due to psychological challenges of living with T1D. The role of the multidisciplinary teams to include psychologists and regular mental health assessments integrated into clinical care are crucial, especially to prepare the young person for transition to adult diabetes services. Agreeing on shared goals and a collaborative care model that incorporates the team working closely together with those living with T1D and their families have been shown to optimise outcomes and quality of life. Early referral, easy access, and affordable psychological care with screening methods in place is associated with lower incident rates of life threatening and compromising diabetes events.

Debate: Should We Screen for and Treat Asymptomatic Coeliac Disease in T1D?

ISPAD guidelines recommend that patients living with T1D should be screened for coeliac disease (CD) every 2–5 years. However, in many areas of the world, patients are not screened if they are asymptomatic. Sensitive and specific serology tests are available but there is limited data to inform as to the risks and benefits of screening and treatment. Evidence suggests that although patients are asymptomatic, they are equally at risk of mucosal damage. Patients developing both T1D and CD are more likely to carry the high-risk genotype HLA-DR3/4 associated with atypical CD and potential CD. The debate of whether to screen asymptomatic children or not raises challenges due to the lack of adequate data and research. Given the challenges and imprecisions, the decision to screen and treat remains in the realm of clinical judgement requiring balanced clinical approaches that provide guidance in the absence of strong clinical evidence.

Symposium – Pushing the Boundaries of TD1 Technology

The introduction of diabetes technologies to those newly diagnosed has proven to be safe, effective and show long-term improvement on HbA1c. Access to CGM and pump therapy is associated with better glycaemic outcomes, increased time in range and lower HbA1c. CGM should be offered to all children at diagnosis and pump therapy is a better alternative to multiple daily insulin regimens with hybrid close loop (HCL) systems being accessible. Family support and diabetes education are important factors when optimising the effectiveness of technology use. It is important to recognise the positive and negative impacts of technology on the child and family. Sleep has been shown to have an impact on physical and mental health, and there is an association between a lack of sleep impact insulin sensitivity, poor

concentration, and an altered behaviour pattern around food and activity. Barriers to technologies such as cost, alarms, and on-the-body experience can be recognised by patients and the family's as negative outcomes of both CGM and pump therapy A solution focus approach can be used as a tool to promote functional and helpful conversations focussing on what is working well as too much pressure upon numbers can negatively affect management impacting time in range and A1c.

Symposium ISPAD-JDRF: Global Paediatric Diabetes Development – What Can ISPAD Members Do?

For people living with T1D today, there are still discrepancies between subjects living in high-income countries (HICs) and subjects living in low-middle-income countries (LMICs). In LMICs, even basic diabetes care like access to insulin, glucagon, blood testing strips and diabetes education is limited. Six million lives could be saved by 2040 if all people living with T1D have access to basic diabetes care from diagnosis. To achieve this goal, new programs are being developed, with advocacy groups whose mission is to support the provision of the best possible diabetes healthcare to all children and youth with diabetes in LMICs. At the same time, clinical research and international advocacy should be conducted, and where recipient LMICs are being helped to achieving sustainability.

Symposium ISPAD-ADA: Diabetic Complications in T1DM

Childhood and adolescence are periods during which intensive education and treatment may prevent or delay the onset and progression of diabetes complications. Focussing on diabetic kidney disease (DKD), microalbuminuria has classically been considered the earliest clinical manifestation. Estimated glomerular filtration rate (eGFR) as a DKD biomarker has been described. EGFR is able to detect both declining kidney function and hyperfiltration, preceding the onset of microalbuminuria. Unfortunately, more studies are needed to develop better eGFR equations for T1D and its validation in the paediatric population. Increasing evidence indicates a relationship between late complications of T1D and epigenetic mechanisms. Long-term hyperglycemia causes aberrant epigenetic marks that persisted even when the normoglycaemic environment was established and maintained, indicating the involvement of epigenetics in metabolic memory. Epigenetic may in future be used as a biomarker for the early detection of micro-and macrovascular complications.

Symposium – Patient-Reported Outocomes in T1D Care

Patient-reported outcomes (PROs) are valuable for shared decision-making. The person with T1D frequently struggles to manage their condition and report suboptimal clinical outcomes. In most clinical trials of T1D, PROs are often neglected. Patients may often have differing perspectives on the impact of medicines or medical devices on their quality of life or other outcomes than those established as formal endpoints in clinical trials in the real world. There is a need for standardisation of PROs to help inform people with diabetes about the expected course of disease and treatment, for shared decision-making with healthcare providers, to monitor quality of life outcomes and to improve diabetes healthcare.

Joint Symposium ISPAD/ESPE: Focus on the Endocrine Pancreas

The pancreas contains besides the insulin-producing beta-cells, also alpha and delta-cells involved in glucagon and somatostatin secretion. In T1D, along with loss of beta-cell function there is an abnormality in glucagon secretion in the forms of hyperglucagonaemia, postprandially increased secretion and impaired secretion during hypoglycaemia. Research has already been conducted in adult patients with T1D and T2D for various agents including analogues of amylin, GLP1, GIP and glucagon and glucagon receptor antagonist. This has shown promising results across a number of parameters including measures of glycaemic control and glucose level excursions. These could help inform future research questions in the paediatric population and the possibilities of other treatments beyond insulin.

Joint Symposium ISPAD-ATTD

The recent advancements have enabled identification of individuals who are antibody-positive in pre-clinical stage 2. The purpose of monitoring is to prevent diabetic ketoacidosis at the onset of clinical stage 3 T1D, and to guide the initiation of insulin treatment. Recommendations state

that patients in stage 2 T1D must be managed by diabetologists and is relevant for both research, clinical monitoring, and treatment initiation. Clinical decision support systems are increasingly being used with the advancement of automated insulin delivery systems. Adjustments of pump settings and insulin dosing were shown to be non-inferior to physicians when based on artificial intelligence algorithms. Obesity is increasing in the paediatric population and treatments must be initiated to reverse this epidemic before adulthood. Healthcare professionals have a role in determining causes for obesity including rare biomedical causes and identification of comorbidities. Treatment should be initiated where combined lifestyle interventions are prescribed primarily, and pharmacotherapy used as a secondary add-on to the lifestyle interventions.

Symposium – Keeping It Cool with Insulin

Access to insulin into LMICs is complex, and there are global and national issues that impact on availability and affordability of insulin. Published evidence of thermostability over the past 40 years had been scarce and based on animal derived insulin. Most of the commercial insulin used is marketed as suitable for use for only up to 4 weeks once taken from the refrigerator and if kept at 30 degrees or less. Based on earlier investigations of the efficacy of non-refrigerative methods of cooling influenced by traditional practices globally (e.g., clay pots and goat skins), a study from a region in central India presented real-world evidence of evaporative cooling of insulin. Various insulins were stored for 4 months via specially designed clay pots in comparison with both refrigerated and non-refrigerated samples. The results showed insulin could be kept below the recommended 30 degrees in a harsh climate with peak temperatures of 42.2°C, with no more than 5% reduction in potency as found with high-performance liquid chromatography and nuclear magnetic resonance spectroscopy analysis methods. This area of work has promising implications for patients in resource-limited settings where temperature is an important concern environmentally.

Symposium – Diabetes Registries Are Not Only for Researchers: How and Why to Start

Participating in diabetes registries help to compare outcomes, highlight variations in care and define challenging objectives while improving care through exchange of experiences with other centres. SWEET registry is an international project established in 2008, currently with 154 centres in 62 countries, created to improve outcomes in paediatric diabetes through benchmarking. The Registry of People with Diabetes with Young Age at Onset in India was created to understand the disease pattern, geographical variations, and burden of complication. CENDA is a national paediatric diabetes registry started in Czech Republic 10 years ago. They consider technology, education, and organisation of diabetes care the pillars to improve T1D control and life prognosis in children. The common notes from these three registries include the ability to report on a wide range of parameters such as characteristics of the population, risk factor control, complications, treatments, and costs, and identify gaps in implementation of evidence-based guideline recommendations and need for education.

Symposium – Diabetes Management in Schools

Enhanced measures are being integrated to promote safety and improved living conditions for students with diabetes within educational environments. Given their substantial time spent within these settings, it is imperative that educational personnel undergo T1D training and education. Various studies are actively seeking insights to optimise diabetes care within educational institutions worldwide. A recent study in Pittsburgh, studied the difference in time in glucose target range between the school day, the weekend and during the virtual school during the COVID pandemic. The study highlighted the importance that the school day routine plays a beneficial part in the day-to-day management of T1D. School staff need written diabetes healthcare plans and the support from the diabetes teams to be able to support the individual.

Symposium – Innovations in T2D

Approach to T2D includes considering social health determinants, paediatric bariatric surgeries, and recent therapeutic breakthroughs. Disparities can be attributed to socioeconomic factors, linguistic barriers, cultural nuances, healthcare biases, and individual perceptions of illnesses. Healthcare professionals are urged to exercise sensitivity, acknowledging the significance of linguistic nuances. There is a continuing increase in the children being diagnosed with T2D and further research is needed in this population. There are many more treatment

options available to adults living with T2D, and challenges in T2D research in children and young people are often due to fewer numbers available for studies, lack of resources and needing multiple centres to take participate in the studies.

Symposium – Small Children Big Challenges in Diabetes Management

Eating habits are determined early in life and preferences change over time, which can be influenced by biological, social and environmental changes. Establishing eating habits and routine early is important as young children can develop neophobia (fear of anything new) and can often be reluctant to try unknown foods. It is important to promote healthy eating behaviours in those early years, which can often include; positive parental feeding, eating together, maintaining a healthy home environment and the pleasure of eating. Healthcare professionals need to be aware of differing socioeconomic status in relation to eating habits and availability of certain foods. There are specific challenges around eating habits in young children living with T1D, such as difficulties with carbohydrate counting, insulin dosing and fear of hypoglycaemia. It is important the diabetes teams work with the family to help establish a positive relationship around mealtimes, utilising diabetes technology if available. The offer of parental support is also important, including support groups for parents of young children with T1D. Diabetes technology such as insulin pumps, CGM, and automated insulin delivery systems are particularly useful in pre-school children in reducing hypoglycaemia and glycaemic variability as well as the potential to reduce parental anxiety and improve sleep.

Symposium – Guideline Updates Recent Advancements

ISPAD has introduced major updates in diabetes ketoacidosis (DKA), management in children who require surgery, and hypoglycemia clinical management guidelines. Biochemical criteria for DKA diagnosis have been revised from 15 mmol/L of bicarbonate to 18 mmol/L to increase the sensitivity of diagnosis with a specificity of 91.8%. From the FLUID trial of 1389 DKA episodes, ISPAD 2022 guidelines have recommended fluid liberalisation protocol to avoid under-dehydration-related complications. During major surgery, an intravenous infusion of dextrose normal saline with an infusion of insulin is advised. In case of minor surgery and unexpected hypotensive episodes, 0.9% sodium chloride is indicated. Discontinuation of oral medication on the day of surgery in T2D should be noted and advised to restart after resumption of oral intake. 50% dose reduction in basal and short-acting insulin doses and changes to normal release preparation from extended-release preparation is advised in bariatric surgery.

Symposium – Diabetes and Exercise

Exercise is a cornerstone in the management and mitigation of cardiometabolic risk for children with T1D. Guidelines for physical activity are similar for all children, including at least 60 min per day of moderate to vigorous activity. Recent systematic review showed that youth with T1D are less active than healthy peers with reduced cardiorespiratory fitness. Data from Type 1 Diabetes Exercise Initiative Pediatric Study (T1DEXIP) showed that during exercise, greater drops in glucose were noted in youth with lower baseline HbA1c and shorter disease duration. Nocturnal hypoglycaemia is more likely with prolonged daily activity >60 min per day. To combat hypoglycaemia, current strategies involve adjusting insulin doses before and after exercise Current evidence suggests that HCL performs optimally when meals are announced and reduces the need for precise carbohydrate counting. Disordered eating behaviour also affects 20–30% of individuals with T1D, particularly adolescent females, leading to poorer glycaemic outcomes.

Symposium – Nutrition

Carbohydrate counting is associated with better metabolic control and quality of life, but can sometimes be a burden for children and their families. Current evidence suggests that HCL performs optimally when meals are announced and reduces the need for precise carbohydrate counting. However, HCL may lead to unhealthy eating habits and weight gain. Disordered eating behaviour affects 20–30% of individuals with T1D, particularly adolescent females, leading to poorer glycaemic outcomes. While tools for identification are available, implementing them into clinical practice remains a challenge. Risk factors such as age, gender, body dissatisfaction, eating disorders in the family, and warning signals such as suboptimal glycaemic management, missing visits, systematic calculation of calorie values should be evaluated during visits.

Symposium – Mind the Gap: Guiding Young People with Diabetes into Adult Care

The transition process is a process that requires planning and coordination between team. Implementation of a structured healthcare transition process is associated with positive outcomes in population health, experiences in care and healthcare utilisation. In preparation for transition, issues such as self-management, driving, alcohol, smoking, sex, pregnancy, travelling, and career planning should be discussed, taking into account the age period. The young person should be evaluated for read for transition with various scales (TRAQ, RISQ-T, READDY) and repeated annually if necessary. Issues such as metabolic control, comorbidities, family characteristics, and diabetes distress should be discussed with the adult care team when the patient is transferred.

Conflict of Interest Statement

All the authors declare no other conflict of interests.

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