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ISPAD Annual Conference 2021 Highlights from the ISPAD Roving Reporters Team

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1 | OPENING LECTURE—100 YEARS OF INSULIN

In 2021, the world celebrates together the 100th anniversary of the discovery of insulin. Frederick Banting and Charles Best, a team of Canadian researchers discovered the miracle molecule of insulin and ignited a century of ground-breaking innovations in diabetes care that have since saved countless lives; a treatment that transformed type 1 diabetes (T1D) from a once-fatal diagnosis into a chronic, medically manageable condition. Leonard Thompson, a 14-year-old boy who weighed just over 29 kilos, becomes the first person with diabetes to be treated with insulin. After receiving injections of Banting and Best's extract (described as a "thick brown muck"), Leonard's blood sugar drops. Beyond its immediate therapeutic impact, insulin has served as the centerpiece for incredible advances in the fields of crystallography, molecular biology, prohormone processing, autoimmunity, physiology, precision health, and genetics, while forming the basis for four Nobel Prizes. In honor of this centennial, we commemorate the unlikely scientific journey that led to insulin's discovery, the advances in the knowledge of the insulin molecule that has permitted new insulin-based therapeutics, and the parallel clinical discoveries that have forged our contemporary understanding of diabetes classification and etiology. The transformative discovery of insulin, in part, represented an inevitable culmination of a body of work performed by many investigators over many years, which opened the door to a greater and better world for individuals with diabetes; the evolution of understanding of diabetes pathophysiology occurred at same time. As we look toward the future, we see new treatment innovations that could bring greater flexibility and a more holistic approach to diabetes care. Once-weekly basal insulin, new digital health solutions, transformational stem-cell therapies, and even the hope for curative treatment someday are all part of our effort to defeat diabetes.

2 | PLENARY SESSION I—DIGITAL VIRTUAL DC—THE ONGOING REVOLUTION

Telehealth is the delivery of health-related services and information via electronic/telecommunications technologies aiming to improve patients' health status. Telemedicine could be either asynchronous "store forward," synchronous or remote monitoring. Telemedicine has played a role in diabetes care for decades. Asynchronous services in diabetes care included review of uploaded data from insulin pumps

and continuous glucose monitoring system (CGM). The synchronous or real-time interactive services include real-time videoconferencing for diabetes management. Diabetes remote monitoring included remote monitoring of CGM and hybrid closed-loop devices. Data from different studies, evaluating the impact of telemedicine on diabetes care, demonstrated that telemedicine improved glycemic control, reduced diabetes burden that together resulted in greater treatment satisfaction. Before the COVID-19 pandemic, the uptake of telemedicine was slow and the use of telemedicine grew rapidly during the pandemic. Many diabetes clinics adapted quickly to integrate telemedicine into routine practice during the pandemic, videoconferencing visits temporarily replaced in-person outpatient care in early 2020. Future of telemedicine would include telemonitoring with automation of remote monitoring of CGM data and automated decision support that will help providers make insulin adjustments (e.g., DreaMed AdvisorPro) and also facilitate insulin adjustments (asynchronous, synchronous interactions).

3 | SYMPOSIUM I—NUTRITION IN DIABETES

Paradigms of diet in T1D should focus on both individualized structured eating with weight management as well. The FLEX trial evaluated 109 youth with T1D with 200 days of dietary recalls and overly CGM data. Those adhering to 0–1 structured eating "tenets" had lower percent time in range, higher percent of both time in hypoglycemia at night, and time above target compared to those adhering to two or more tenets. The My Plan Pilot evaluated the feasibility of individualized structured eating patterns. Results demonstrated that progress was made toward alignment of structured eating over the 5-weeks, with high self-reported acceptability. In order to address overweight and obesity, individuals were randomized to a hypocaloric low-fat diet, hypocaloric low carb diet, or Mediterranean diet with no caloric restrictions. Preliminary data demonstrated a statistically significant reduction in weight, BMI, and percent of fat mass with no significant change in HbA1c, percent time in clinical hypoglycemia, or percent time in range over the 3-month period.

Nutrition management in type 2 diabetes is the cornerstone of diabetes care and management. Specific recommendations include involving the family in setting nutrition goals, focusing on reducing excessive energy intake by addressing food portions, avoiding unstructured eating patterns, dietary modifications and negotiation for healthier food swaps. Low carb and very low calorie ketogenic diets can be effective, but require close supervision by an interdisciplinary team. GLP-1 receptor agonists are starting to be used in teens to regulate appetite and maintain weight, but there are still challenges with side effects, acceptances, and long-term use.

Avoiding nutrition burnout is important and adapting tools assessing diabetes burnout can serve as an initial screener for issues related to nutrition. Assessing for nutrition burnout should be done with a psychologist and nutritionist if possible, and strategies to address nutrition burnout include finding support through diabetes associations, disconnecting from social media, asking for help from various resources, and aiming for consistency rather than perfection.

4 | SYMPOSIUM II—SKELETAL GROWTH IN PEDIATRIC DIABETES AND OBESITY (ESPE)

There is an emerging awareness that diabetes adversely affects skeletal health and that T1D affects the skeleton more severely than type 2 diabetes. Studies in humans have identified a number of skeletal abnormalities associated with T1D, including deficits in bone mineral density and bone structure, reduced bone formation and impaired microarchitecture of the bone tissue. T1D is associated with increased risk of fractures across the life span; and fractures were associated with increased age and high HbA1c levels.

Vitamin D (25OHD) has a key role in stimulating calcium absorption from the gut and promoting skeletal health, as well as recognized Immunomodulatory function. Prospective studies are inconsistent whether vitamin D prevents form preclinical or clinical T1D diabetes, gene interactions may explain part of the controversy. Promotion of vitamin D intake in the total population should be recommended and avoidance of deficiency especially in individual at increased risk of developing autoimmune diseases.

Physiology of growth and hormones that influence growth in the context of obesity are described with BMI as the surrogate marker of obesity. Growth is a nonlinear phenomenon with rapid growth velocity occurring in infancy and later again during puberty. In obesity there is accumulation of excess adipose tissue and this is associated with increased ghrelin which stimulates insulin and increased leptin which stimulates growth hormone secretion. Adiposity and obesity is also associated with earlier puberty and premature adrenarche and obesity is also associated with advanced bone maturation, accelerated linear growth, and potentially impaired final adult height. Other factors are also associated with impaired and advanced bone maturation such as IGF1, hypertension, HOMA, gender, and ethnicity.

5 | PLENARY SESSION II—DIABETES PATHOGENESIS

New insights in the field of immunopathogenesis reveal that T1D results from loss of immune homeostasis in between the regulatory T cells (Treg) and effector T cells (Teff), which leads to Teff infiltration of the pancreas, insulitis, beta cell death, and insulin deficiency. Progression of islet autoimmunity into clinical T1D is variable and dependent on the degree of altered immune tolerance. Treg phenotyping revealed that slow progressors have higher insulin-specific Tregs. In addition, the onset of autoimmunity is characterized by impaired Treg induction and stability.

In-vitro studies have revealed that miR142-3p, miR181a-5p and miR92a-3p, regulate cellular states in T cells. Murine studies in the NOD model and human islets revealed decreased abundance of

TET2+ CD3+ Tcells in incipient autoimmunity. TET2 has been identified as an enzyme necessary to prevent methylation of CNS2, a non-coding sequence in the FOXP3 gene, critical in maintenance of the Treg phenotype. Methylation studies in murine and human islets reveal increased methylation of FOXP3 CNS2 in Treg cells during autoimmunity. In-vivo and In-vitro inhibition of miR142-3p leads to increased abundance of TET2, decreased methylation of FOXP3 CNS2, enhancing Treg induction and reduction of islet autoimmunity.

Recently, digital pathology software such as image analysis tools allowed for automated analysis of a multitude of pancreatic islet cells at once, which may generate new findings on the pathogenesis of T1D. In children with recent-onset diabetes, cytotoxic T cells (CD8+) but also other types of T cells such as CD45+, CD68+ macrophages, and CD20+ B cells. The pattern of immune cell infiltration and levels of inflammation vary over time as pancreatic islets are being destroyed, as well as between individuals of different "endotypes," People of the endotype 1 are more likely to be diagnosed at a young age and show higher rates of immune cell infiltration in their islets, with higher levels of CD20+ B cells and aberrant proinsulin processing compared to people of the endotype 2, with older average age at diabetes onset and lower presence of CD20+ B cells. Furthermore, the proportion of residual insulin-containing islets is lower in endotype 1 children of younger (0–6 years of age) than in children with older age (>13 years of age) at diagnosis.

6 | SYMPOSIUM III—ADVANCES IN BIOMARKERS OF T1D (ATTD)

Advances in biomarkers pave the way for better understanding of the pathogenesis of T1D and could provide possible insights for therapeutic and interventional targets. Exendin for β-cell imaging (GLP-1R scanning) enables insights about β-cell mass through a radiolabelled procedure. Studies highlighted a linear correlation between specific pancreatic update and β-cell mass. In clinical setting exendin PET scan is better in delineating β-cell mass. Exendin imaging was found to be safe and feasible in children with low radiation exposure. The extracellular vesicles containing microRNAs (miRNAs) (EVs miRNAs) are often evaluated as biomarkers in health and disease condition; however, their role in T1D is still not fully understood. A three-step study evaluated the role of EVs miRNAs among patients with T1D and Langerhans Islet transplantation. Data showed differential expression of plasma EVs miRNAs in T1D and beta- cell destruction. EVs miRNAs were found to accumulate in endolysosomes and phagocytes with potentially trigger TLR7/8 signaling cascade modulating immune response resulting in proliferation, cytotoxicity, and cytokine release which might contribute to autoimmunity and beta-call destruction in T1D; emphasizing the role of EVs miRNAs as both biomarker and possible mediator in T1D. Being a highly heritable disease with more than 70 regions in the genome robustly contributing to the risk of T1D, genetics plays an important role in its prediction and screening aiming to prevent life-threatening DKA at diagnosis and paving the way for intervention trials. HLA typing and Family history could predict risk of developing T1D by 10%–50% by age of 20 years, however the need to increase sensitivity of genetic prediction triggered the development of Genetic Risk Score (T1D GRS).T1D (GRS) could be the starting point for future prospects for population-level prediction studies.

7 | SYMPOSIUM IV—DIABETES CARE AND MIGRATION (JDRF)

Current immigration flow reflects moving from low to high T1D incidence. Earlier occurrence of T1D in immigrant children is probably due to the existence of some environmental determinants acquired with a more westernized lifestyle. Environmental triggers of disease onset have been identified through several longitudinal studies of large at-risk cohorts. Environmental determinants of diabetes include infections, exposure to cow's milk, early exposure to dietary gluten, factors influencing gut microbiota, and toxic chemicals affecting β-cells.

Diabetes care among the heterogeneous group of immigrants faces a set of challenges. Challenges include accessing healthcare, communication difficulties, family dietary habits and health beliefs, acculturation and degree of assimilation. Clinicians must assess patient's health literacy, use professional interpreters, provide information in the native language, and adapt content so that it is culturally sensitive. Lack of access to healthcare and new technologies has been reported in multiple countries including the UK, Germany, and Austria. Possible reasons include financial barriers, lower rates of acceptance for new technologies, issues with health literacy, clinician bias or discrimination, and inability or willingness of team to adapt training. To address acculturation, clinicians should seek to promote the traditional values and habits of families and reinforce traditional dietary habits.

Regarding the Middle East experience, common challenges include limited experienced healthcare professionals, usage of premixed insulin at diagnosis, and infrequent glucose monitoring. The main challenge-affecting migrants is accessing healthcare. In a study comparing migrant and Jordanian children with T1D, data showed significant difference between both groups in terms of lack of medical insurance, less income and less education among migrants. There was no difference in terms of HbA1C or insulin regimens. Although, migrants had more DKA at presentation, recurrent DKAs, and hypoglycemia, but these did not reach statistical significance. Almost half of migrants did not know the status of celiac or thyroid disease.

8 | SYMPOSIUM V—DIABETES IN THE COVID ERA (ADA)

Many children with T1D have been affected by the COVID-19 pandemic; whether new-onset, or established T1D. COVID-19 can impact T1D progression at the level of immune activation, immune response, accelerate progression from Stages 1 to 2, or Stages 2 to 3. However to date, there are no clear epidemiological data on an increased

incidence of T1D during the pandemic. Published data show that a good number of children had a delayed diagnosis due to delayed presentation to healthcare system, wrongly diagnosed, and other COVID-related problems.

The majority of studies showed that DKA at T1D onset was higher during COVID-19 lockdown period. Moreover, the rate of severe DKA at onset has increased. This has been postulated to be due to limited access to healthcare leading to more severe presentation. In addition, cytokine storm with COVID-19 could injure β-cell reserve in those nearing Stage 3 accelerating disease progression. Other mechanisms have been suggested, such as direct destruction of β-cells by SARS-CoV-2 virus causing an increase rate of T1D progression and DKA-without evidence of autoimmunity. Yet, no increase in frequency of antibody-negative T1D in Germany has been observed. The effect of COVID-19 on DKA in established T1D seems to be less pronounced than those newly-diagnosed.

COVID-19 highlighted the importance of application of telemedicine and telemonitoring via CGM for people with DM. Recent CGM data showed that glycemic control of children and adolescents with T1D improved during the lockdown, especially in those with hybrid closed-loop. The improvement in TIR in several cohorts (with a median change of 3.3%) was shown to be due to greater parental care, better diabetes self-management, changing meal and sleeping patterns, socioeconomic status, and more physical activity. Finally, further studies and robust research funding are still needed to learn more about the impact of COVID-19 on T1D.

9 | SYMPOSIUM VI—PSYCHOSOCIAL ISSUES IN DIABETES

Integrating psychology as part of the core diabetes team is important and often the service is there but the access is difficult with location of the psychologist being away from the diabetes team and waiting times too long. There also remains stigma related to seeing a psychologist. Accessibility, flexibility, and integration needs to be a priority. Interdisciplinary approach with the psychologist being with the diabetes educator or diabetes dietitian can help improve accessibility and screening and also establish rapport and reduce stigma.

Burnout is a collection of feelings related to looking after diabetes day after day with no break. There are high rates of burnout among teens, young adults, as well as caregivers. Burnout is closely linked to anxiety and depression. SEARCH Study, a large prospective study evaluating the levels of stress, depression and quality of life among a cohort of teens with both type 1 and type 2 diabetes, emphasized that diabetes has an impact but for different reasons in type 1 versus type 2. Psychosocial screening is important to identify the behavioral and emotional correlations of diabetes management which will provide ultimate care with subsequent improvement of health outcomes and reduction of health costs and burdens.

The language we use and in addition, all forms of communication such as images and tones matter and hence #languagematters is trending. It's important for healthcare professionals to remove judgment and stigma towards the person with diabetes. Many complain that they feel like they have failed, blamed, and shamed after leaving session with their healthcare professional. Referral letters and how we word them even between healthcare professionals needs more reflection and review. Focusing on the positives is where you turn the thinking and change attitudes. Diabetes self-management is so hard we need to celebrate the wins, small or big.

10 | SYMPOSIUM VII—OTHER FORMS OF DIABETES IN CHILDREN AND ADOLESCENTS

Advances in genetic testing has shed the light on the use of precision medicine in monogenic DM. Genetic screening should be done in autoantibody-negative individuals with T1D as 6.5% of them may have a monogenic cause. Variant interpretation may be difficult; therefore, additional functional studies may be necessary to predict variant pathogenicity. Although HNF1A-MODY is known to be sensitive to oral SU with an increased C-peptide response to oral or intravenous glucose tolerance tests, testing the function of rare HNF1A variants showed reduced SU effect.

Overweight and obesity are increasingly common in youth with T1D; which has led to coexisting features of T1D and T2D "double diabetes." The accelerator hypothesis has proposed that weight gain is the missing link between T1D and T2D. However, further research is needed to explain how obesity contributes to islet autoimmunity and T1D pathogenesis. Adequate counseling on a healthy diet and physical activity are crucial in the diabetes care to prevent excess weight gain and its consequences. There is limited evidence for any beneficial effect of adjuvant therapies on glycemic control in children with T1D.

Cystic fibrosis-related diabetes (CFRD) is unique and different from T1D, and T2D. ISPAD guidelines recommend annual OGTT for all patients with CF at age ≥10 years as a standard screening test for CFRD. However, CFRD is usually asymptomatic and about 33% are missed on OGTT alone. CGM has been validated for use in CF children and adolescents, it can detect abnormal glucose tolerance earlier than OGTT so can aid in the diagnosis, and help in day-to-day insulin adjustments. The future is bright for CFRD as new CFTR modulators, for example, Kaftrio show promising results with improvement in glycemic control; however, further RCTs are needed in children with CF.

11 | SYMPOSIUM VIII—NOVEL THERAPIES FOR T1D

Different immunological pathways have been acknowledged in the pathogenesis of T1D; paving the way for T1D immunotherapy research. A number of therapeutics (Alefacept, Rituximab, Abatacept, Teplizumab, and ATG) targeting different stages of T1D have been used and were successfully able to preserve β-cells function. Data from T1D TrialNet'S Teplizumab (anti-CD3) prevention study showed that Teplizumab potentially delayed T1D by a median of 2–3 years in

children and adults at high risk. A low dose ATG in Stage 3 T1D is a cost effective therapeutic target significantly preserving C-peptide. COVID-19 impacted immunotherapy research in T1D; however it is important to precede with therapeutic interventions especially those with low relative risk. The therapeutic approach of stem cell research holds great promise for the cure of T1D.Identifying different mediators and transcription factors are essential in defining β-cells identity. MAFB, a transcription factor specific to human β-cells, plays a crucial role in the development of glucose-responsive β-cells from pluripotent stem cell. BOLA3, a regulator of aerobic respiration within mitochondria, is important mediator in mitochondrial β-cells and its elimination affects β-cells identity and function. Advances in insulin formulations modulating its pharmacokinetics would provide a platform for generation of more stable ultra-fast insulin. Beside loss of beta cell function in T1D, there is deficiency of amylin which acts in a synergistic manner with insulin to control postprandial blood glucose. A novel insulin-amylin co-formulation would provide a more physiologic profile of insulin. Both ultra-fast insulin and insulin-amylin co-formulations could mimic the regulatory function of the pancreas. Personalized medicine with early Intervention and treatment using novel therapeutic targets represent paradigm shift in managing T1D.

12 | PLENARY SESSION III—BRIDGE TO THE NEAR FUTURE

Bridging the near future with state of art in closing the loop.

"WeAreNotWaiting" is a community of people with diabetes that wanted to develop Do It Yourself artificial pancreases (DIY APS) as an unmet need. DIY APS ideas have been developing for a long time but the noise around social media of people successfully using the DIY devices has make a difference now. "WeAreNotWaiting" will be "What's next" where this movement will look at other unmet needs.

Hybrid closed loop (HCL) Systems comprise three key elements: glucose sensor, control algorithm which analyses the data and instructs the insulin pump. The system works very similar to the beta cells in terms of amounts of insulin. HCLS reduces the burden of diabetes in both the user and the family. In addition, it is easier to achieve the time in range goals and low hypoglycaemia exposure. Regarding burden, it is meant to be low with a user interaction of 10–20 min a day, low alarm burden and low technical difficulty. At the moment the commercially available systems are CamAps FX, Diabeloop Roche, Medtronic 670G and 780G and Tandem Control IQ. Upcoming systems are Omnipod Horizon, Tidepool Loop, and Beta Bionic iLet. These systems have variable recommended users according to age. At the moment CamAPS is recommended for children over 1 year of age while Tandem and Medtronic 6 and 7 years, respectively. The closed loop systems still need a certain level of optimization. It is important to take a structured approach to data review and understand the settings that need to be adjusted according to the system used. Defining goals and discussing expectations are important. Also consider the alarm burden and mental health.

13 | SPECIAL EVENTS

13.1 | #DOCDAY: What we wish you knew—And why

Under the mantra #NothingAboutUsWithoutUs, the #dedoc voices scholarship program enables patient-advocates to participate in diabetes conferences. The #dedoc voices represent a network of like-minded peers who mentor, coach and support their advocacy work. They participate in scientific sessions and industry symposia to discuss, curate and translate what they consider as relevant and share their learnings in a way that is understood and appreciated by people with diabetes and the Diabetes Online Community around the world. The program further provides a dedicated platform for people with diabetes, healthcare professionals, researchers, and the biomedical industry to network, through #docday, a format with short presentations and pitches and #docnight, an informal get-together.

ISPAD 2021 was the first scientific conference to host a #dedoc symposium with patient voices as presenters. Both chair and presenters of the session titled "What we wish you knew—and why" were people living with T1D, members of the #dedoc voices program and active diabetes advocates. The talks covered patient involvement in research, #LanguageMatters, peer-support, and access to insulin and diabetes education in the developing world.

The active participation of patient-advocates in the virtual conference was welcomed by the conference organizers, followed by the audience with great interest and may serve as a role model for patient and stakeholder engagement in future scientific meetings. For their upcoming activities, Bastian Hauck, founder of #dedoc, and Emma Doble, patient editor of the BMJ, announced their collaboration for a special article collection titled "what your patient is thinking," to which the #dedoc voices will actively contribute.

13.2 | Exercise around the world—LOD symposium

The League of Diathletes is a network of diabetes grassroots organization in different parts of the world founded by Gavin Griffiths (UK). A panel of seven speakers shared their experiences about exercise and diabetes management covering the topics of access to technology and exercise, mental health and exercise, overcoming physical challenges with diabetes and the role of healthcare providers around exercise and T1D education. The panel was composed by participants from the UK, Costa Rica, India, Kuwait, and France who had a passion or knowledge about exercise. To overcome barriers to exercise, the proper diabetes education on how to handle exercise is important and it is essential to have the right support and motivation to use the tools you have access to. Whether using diabetes technology or MDI (multiple daily injections), it is important to adapt to what your body needs when speaking about exercise. The use of diabetes technology can have a positive impact on HbA1c and helps train better, recover quicker and ultimately led to better sport performances. For the best outcome, the multidisciplinary team working together

(including dietician, psychologist, nurses, PE teacher, etc.). At the end of the symposium, all panelists were asked for one word to describe diabetes and exercise. The words given were commitment, rollercoaster, unpredictable, passion, defiance, teacher, and life.

All presentations are available on the ISPAD website Conference Resources Platform: https://medialibrary.ispad.cyim.com.

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