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WILEY ISPAD International Society for Pediatric and Adolescent Diabetes

ANNOUNCEMENT

ISPAD Annual Conference 2016 Highlights†

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DIABETES AT 212 DEGREES: CONFRONTING THE INVISIBLE FOR THE NEXT GENERATION

Is diabetes hot enough, or do we need to truly light a fire? It is sometimes necessary to find new approaches to obtain a higher goal. A large percentage of children with type 1 diabetes (T1D) still present in diabetic ketoacidosis, and a large number of youth do not achieve targets for diabetes control. There is a change in the characteristics of patients with T1D (younger, higher body mass index [BMI], different human leukocyte antigen [HLA] genotype) and in many places diabetic ketoacidosis is also increasing. Insulin is not a cure and much is needed on advocacy, education and research for diabetes worldwide. Our goal is to cure and prevent diabetes, do not adjust the goals, adjust the actions steps!

GENETICS AND ENVIRONMENTAL FACTORS

The balance between destructive and protective genes will determine the destruction of beta-cells. Genetics of diabetes allows identification of mechanisms of disease, defining genetic risk, defining genetically at risk cohorts for natural history studies (TEDDY, DAISY, BABYDIAB) and ultimately the primary prevention of diabetes.

There is still work to be done in the environmental triggers for T1D, and no "smoking gun" has been identified yet, although the evidence is mounting for a role of enteral virus infections. There is well documented upregulation of major histocompatibility complex (MHC) class I in association with T1D. Therapies will be needed at an antigen-specific level, and in association with a range of current or considered therapies (Glucagon-like peptide-**1** [GLP-1], anti-inflammatory agents, anti-T- or B-cell agents).

Understanding the legacy of hyperglycaemia in diabetes: *metabolic karma*; "Good karma"—efforts today have long-term pay-back. Metabolic control diminished diabetes complications both in the DCCT and EDIC, or, in other words, showed positive Karma for those better controlled from the beginning of the disease. Linking epigenetic changes to hyperglycaemia induces changes in gene expression, and understanding the histone code will no doubt provide more clues to come.

AUTOIMMUNITY AND DIABETES

Type 1 diabetes (T1D) has a long asymptomatic phase before progressing to a metabolic disease, the presence of multiple autoantibodies against beta cells has a life time risk of developing T1D approaching 100%. The Fr1da screening study in Bavaria, using a novel capillary test for GADA, IA-2A, and ZnT8 has to date screened 50 000 children <6 years of age and 165 (0.33%) have stage 2a T1D (early diabetes).

Use of metformin in addition to insulin therapy failed to improve glycaemic control in 6 months in subjects who were overweight, had a family history of T2D, had high insulin requirements and showed signs of insulin resistance. Metformin was effective in reducing insulin requirements and BMI and low density lipoprotein (LDL) cholesterol.

†The 42nd annual ISPAD meeting took place from 26 to 29 October in Valencia, Spain. The roving reporters present an overview of the scientific highlights of the meeting. Videos of presentations are available on line: http://2016.ispad.org/

The etiology of celiac disease is associated with HLA-DR3-DQ2 and non-HLA genes. The amount of gluten consumed until 2 years of age increases the risk of celiac disease. A 2-hit hypothesis indicates that gluten and virus infections may play a role in the pathogenesis.

JDRF SYMPOSIUM EXERCISE

This symposium highlighted the integral role that nutrition plays in the management of T1D especially for peak exercise performance. As well as a strong support team, a balanced lifestyle includes: proper nutrition, adequate sleep, academic development, psychological well-being. Insulin adjustment strategies and flexibility are important to ensuring safe, effective, and optimal sports performance.

Both hypo- and hyperglycaemia have multiple deleterious effects on exercise performance. Exercise is challenging due to nonphysiological insulin treatment, variable effects of exercise types, timing of insulin action, competitive stress, fear of hypoglycaemia and inter- and intrapatient variability.

ESPE/ISPAD SYMPOSIUM: RARE DIABETES

Registries are essentials for rare diseases, EuroWABB Registry is a project to try to gather information about Wolfram, Wolcott-Rallison, TRMA, Allstrom, and Bardet Bidel Syndromes, with the objective to better understand and treat these conditions, as well as support access to genetic testing.

Neonatal diabetes can be caused by mutations in KCNJ11. Treatment with sulphonylureas (SU) started in 2004 and a new long-term follow-up study is being done with 79 patients from different centres, with the objective to evaluate efficacy, metabolic control, mortality, and other factors related to diabetes.

Prevalence of Berardinelli-Siep syndrome (congenital generalized form) and other lipodystrophies is 10 to 40 cases per million, patients present with decreased amount of subcutaneous fat, generalized or partial, congenital or delayed. It is associated with insulin resistance, diabetes, hypertriglyceridemia, acute pancreatitis, and liver steatosis, risk of cirrhosis, hyperandrogenism and PCOS.

TYPE 2 DIABETES (T2D)

Type 2 diabetes (T2D) is still a disease ultimately of beta cell failure. In the TODAY study (Treatment options for type 2 diabetes in adolescents and youth); metformin alone was not enough to maintain glycaemic control. The high percentage with positive T1D antibodies also makes it important to check antibodies in all youth with suspected T2D.

Childhood obesity is a multifactorial, complex disorder; including media, transport, family, government, school environment and lack of control, even where people live—socioeconomic predestination. Strategies include nudging, (no sweets near checkouts) and designing environments to make healthy choices more available or passive and active energy expenditure.

OBESITY AND INSULIN RESISTANCE

Insulin resistance, impaired beta-cell function, and impaired incretin effect constitute the pathophysiology of youth pre-diabetes. The problem of translating the complex pathophysiology and measurement of insulin action production and translating to simple, clinic based and reproducible testing is paramount. In youth there is faster decline in beta cell function than in adults with T2D.

Obesity is associated with poor executive function, a complex system of cognitive schools. Working memory, cognitive flexibility, and reasoning is related to obesity; a potential target to improve educational attainment.

Early life nutrition and catch up growth of the infant born SGA is characterized by a recovery of lean mass. Potentially detrimental effects of enriched formula on cardiovascular risk factors and potential for overweight to aggravate this long term are a real concern.

IMPROVING DIABETES IN EMERGING ECONOMIES

Current programs to improve diabetes care focus on attaining a multidisciplinary team of doctors, nurses, psychologists, nutritionists, and so on. Some areas have difficulty financing diabetes treatment. Intensive, continuing education is emphasized and use of phone or technology-based means of communicating treatment has been shown to benefit patient care.

ADA/ISPAD SYMPOSIUM: EMERGING DIABETES THERAPEUTICS

To facilitate the treatment of neonatal diabetes with KCNJ11 mutations, oral suspension of glibenclamide is as effective as crushed tablets and more convenient to the patients.

T1D starts with the development of the double antibody state, and clinical progression is highly dependent on age, with children and young people at much higher risk of progression to clinical diabetes. The number needed to treat at the 2 antibody stage with an effective therapy to prevent morbidity and T1D is relatively low compared with blood pressure and cardiovascular outcomes for example.

The idea of replacing the pancreas is based on old concepts: regarding isolation of islets and transplant. Difficulties are related to immune response and, specially, fibrosis. Modified alginate has been developed to create spheres with larger size, that are more biocompatible than the smaller ones. New modified capsules proved to be effective in mice and primates, without generating fibrosis.

ECONOMIC BURDEN OF CHILDHOOD DIABETES

The incidence of T1D worldwide is increasing, but does differ around the world. This is expected for a condition that is multifactorial and

has an etiology that involves environmental triggers superimposed on genetic susceptibility.

The economic cost of diabetes includes direct and nondirect costs, and varies in a U-shaped fashion with child age in Spain. Poor glycaemic control increased by 28% the direct healthcare cost of children with diabetes.

BETA CELL THERAPY

There are on-going challenges, whether in the field of donated stem cells (lack of supply, risks of immunosuppression), human pluripotent stem cells (debatable ability to produce adequate insulin at the right time) and macro/micro barrier technology. Tantalizingly close but so far away, it is debatable whether beta cell therapy will forever remain a treatment of the future.

Possible avenues for gene therapy in diabetes including candidate genes that may allow regeneration of the islet cell mass, production of insulin by nonpancreatic tissue, or the prevention of secondary complications.

DIABETES REGISTRIES

Comparisons of multiple registries in different parts of the world highlighted similarities and differences in use of registries among clinics, glycemic control, other diabetes-related health outcomes, and demographic factors. Use of international databases can help pair centres with similar struggles or potential solutions to support each other, increase collaboration, and set the stage for international studies and "open benchmarking."

DIABETES AND MICROBIOTA

The field of microbiota is an enormously complex and intriguing area of active research, with 100-fold more genes in the microbiome than in the human genome. There appears to be a critical development window pertinent to altering the intestinal microbiota that has lasting metabolic consequences, including whether early antibiotic exposure or illness itself shape this interaction. The results of the current RCT's of fecal gut transplantation in obesity, T1D and T2D are intriguingly awaited.

JDRF/ISPAD SYMPOSIUM: NEW TECHNOLOGIES IN T1D

In addition to hardware, there is a spectrum of different approaches to software; from completely open loop (sensor augmented pump therapy, auto suspend, threshold predictive, programmed basal suspend, adaptive basal) to fully integrated closed loop and in turn to complete replacement with multihormone closed loop. Areas of special complexity include exercise, and closing the loop in the very young.

Each patient age group will have its own challenges with increasingly complex technology, so the approach to education should focus on both patients/family and the physician. Good education is fundamental because systems are different from each other.

Future goals include fully automated closed loop and the requirement for faster insulin: incorporating modifications to improve kinetics, intra-peritoneal delivery, and adjunct therapies (glucagon, pramlimtide, SGLT2 inhibitors, GLP1 agonists). The challenges will be with glucose sensing accuracy and lag and infusion set having reduced interruptions and improved longevity.

EMOTIONAL BURDEN OF T1D

Except for rare individuals, most need a team and support to cope with the requirements of good diabetes control; from eating to exercise to exams. Distress is a better predictor of diabetes control than depression; parental distress is associated with low levels of teen-age self-efficacy.

Intensified therapy is not the "Nirvana" we hoped for, pumps are not magical and "not all that is new is better". The questions are "Are we on the same page as our adolescents? Have we set achievable goal for them? Do we have an appropriate circle of influence for them? Should we de dogmatic about outcome, but pragmatic in approach?"

THE STATE OF THE ART ON DIABETES COMPLICATIONS

The developing brain is a target organ in diabetes, synaptogenesis peaks at the average age that diabetes is diagnosed, and in a child takes up to nearly 50% of the basal metabolic rate. Events at diagnosis and glycemic extremes differentially affect the developing brain. Considering the pathophysiology of diabetic retinopathy, it is known that neurodegeneration is an early event, secondary to apoptosis and reactive gliosis. A new therapeutic approach includes GLP1 receptor to reduce reactive gliosis and apoptosis.

DIABETES E-HEALTH

The impact of "closed data-loop" may enable a large improvement in metabolic control and empowering patients. Combined with improving contacts, coordinating with insulin pump therapy, and outlining the lag time of 3 to 6 months to enable engagement of the technology with patients and team.

The Be He@lthy Be Mobile program outlined the ability to bridge the new problems we face with our new opportunities, in particular the internet of everything. Fascinating approach and outlining the adoption of technology and smart phones in particular in

the third world which may be more receptive than some first world centres.

Humans teach skills and survival by games and interaction over millennia, not by sitting in classrooms and with exams, online gaming is the new tool we have to hone and develop this for children with diabetes.

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