ISPAD Annual Conference 2015 Highlights

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The 41st annual ISPAD meeting took place from 7th to 10th of October in Brisbane, Australia as a joint meeting with the Australasian Paediatric Endocrine Group. The roving reporters present an overview about the scientific highlights of the meeting.

Can we put the brakes on Diabetes

Dr Dabelea presented an update on SEARCH data confirming an increase in prevalence for type 1 and type 2 diabetes (T1D, T2D) from 2001 to 2009. The increasing rate of obesity has made it more difficult to define diabetes types, suggesting the need of appropriate classification of diabetes in youth as autoimmune or non-autoimmune, and insulin-sensitive or resistant. Individuals with 'high risk' HLA alleles show a decreasing proportion of new diabetes diagnosis, with lower risk alleles becoming more prominent, suggesting a change in environment rather than genetics per se.

Dr Ortqvist emphasized the importance of early tight control in diabetes with reduction of risk for complications, irrespective of later control. She pointed out the improvements in care achieved by national and international benchmarking, demonstrating reduction in HbA1c with no change in severe hypoglycaemia, and a reduced number of presentations with severe DKA after introduction of SWEDIABKIDS registry. This has been achieved through a number of measures: carbohydrate counting is now standard practice among diabetes patients, the introduction of a board of health and welfare guidelines for diabetes self-care in preschool and school, providing resources for schools, and through effective team-work.

Epigenetics

Developmental origins of health and diseases refers to the mechanism by which events in fetal life can influence long term health (Dr. Ozanne). In animal studies, multiple mechanisms, eg maternal low protein diets, total caloric restriction, uterine artery ligation and maternal obesity, all result in a common diabetic phenotype in the offspring. There are three main mechanisms by which this change occurs: 1. Permanent structural change, as demonstrated by a reduction in beta cell mass, nephron number, or cardiac structure and function. 2. Accelerated cellular aging, indicated by telomere shortening. 3. Epigenetic programming of gene expression through changes in DNA methylation and/or histone modifications. Animal models have revealed reduced interaction between enhancer and promoter regions in offspring of macronutrient-deprived mothers. Post-

translational modifications have also been observed within adipocytes of animal studies and human biopsy samples, with reductions in insulin signalling proteins without changes in mRNA. An understanding of all these mechanisms may give insight into interventional strategies to improve long term metabolic health.
Metabolic memory is the phenomenon by which previous exposure to metabolic perturbations has long-lasting effects (Dr. El-Osta). This is best demonstrated in T1D by the DCCT/EDIC trials, whereby a period of intensive diabetes treatment with improved metabolic control resulted in decreased risk of microvascular complications a decade later, despite similar glycaemic control for the previous decade. This metabolic memory is due to epigenomic changes causing altered signalling and transcriptional changes.

Diabetes genetics, immunology and environment
Factors that trigger autoimmunity and development of type 1 diabetes are being researched to find novel interventions that may prevent this process. Perceived requirement of micronutrient supplementation during pregnancy is common, and there is anecdotal evidence that they are taken over the recommended intake in developed countries. One such example is iron supplementation. Colleagues in Finland found that in their cohort, for each doubling in newborn iron levels the odds ratio for developing T1D increased by 3.28 compared to controls. It was hypothesised that increased reactive oxygen species (ROS) cause β cell destruction. New agents that reduce ROS may have a role in preventing the advancement of antibody positivity to T1D.

VIDIS symposium
What can we learn from pancreatic biopsies?
The understanding of the aetiology of T1D is still limited. Fresh pancreatic tissue from patients at diabetes diagnosis could help in understanding of the disease process. The Diabetes Virus Detection Study (DiViD) has provided new insights into this area (Dr. Krogvold). First, insulin producing live islets could regain their ability to secrete insulin after exposure to a non-diabetogenic environment. RNA for all the genes involved in insulin production was found in the tissue samples. These findings suggested that the cellular machinery for producing insulin is still intact. Second, insulitis was explored. Immunohistochemistry and PCR analysis for RNA showed that Enterovirus Capsid Protein 1 and hyper-expression of Class 1 HLA molecules was detected in all T1D islet cells. These results provide evidence for the presence of Enterovirus in the pancreatic islets of T1D, consistent with the possibility that a low-grade Enteroviral infection contributes to disease progression in humans and may pave the way for the development of possible antiviral medications or vaccines to prevent disease progression. Detailed analysis of the molecular pathology of T1D in samples of human pancreas showed that immunopositivity for the Enteroviral Capsid protein 1 is restricted to the beta cells within the islets in patients with T1D (Dr. Morgan). Beta cells may be able to sustain an atypical and persistent enteroviral infection in those that go on to develop T1D. This may lead to molecular changes in the structure of the viral genome, along with an anti-viral response by the cells which leads to altered antigen presentation. Autoimmune diseases share many genetic and environmental determinants. Identifying combinations of genetic and environmental factors that interact in autoimmune disease may give the ability to explain disease risk profile, and to uncover molecular mechanisms that may contribute to disease

pathogenesis. Environmental effects on immune responses may be mediated by changes in epigenetic regulation, an understanding of these mechanisms may allow for the development of targeted preventative approaches (Dr. Ponsonby).

Hot Topics in the Basic Science Arena

This symposium covered the hot topics in basic sciences to promote a better understanding of disease mechanisms and the development of future therapeutic and preventive drugs. Dr Coughlan provided data on mitochondrial damage as central to the pathogenesis of diabetic nephropathy. Though it is not clear as to whether hyperglycaemia is the perpetuator of this damage, mitochondrial dysfunction is noted as early as 4 weeks in animal models with fragmented mitochondria demonstrated on electron microscopy both in animal and human models.

Dr Hasnain highlighted the importance of cytokines in beta cell function of the pancreas in Type 2 diabetes. High concentrations of lipids and glucose cause endoplasmic reticulum (ER) stress which results in aberrant insulin secretion with increase in proinsulin to insulin ratio. While IL-23, IL-24 are potent cytokines which induce ER stress, IL-22 suppresses this response by regulating oxidative stress modulating genes and restores insulin production. Pre-treatment with IL-22 reduces ER stress and chemokine production, and restores the production of high quality insulin secretion.

Dr Moritz stressed the effect of drugs, especially alcohol on the origins of metabolic dysfunction. Prenatal perturbation affects foetal development and can cause long term programming disturbances with increased risk and susceptibility to diseases in off springs. Alcohol can affect this foetal programming; therefore it is crucial to increase public awareness regarding the effects of alcohol consumption around conception on offspring health.

Complications – Macrovascular Disease in Diabetes in the Young

Dr Couper showed the greatly increased risk of CVD in children diagnosed with diabetes, particularly in females who have a 7-fold increased risk of death from CVD. Identifying markers of cardiovascular disease is the first step in being able to intervene. In children, non-invasive measurements of cardiac function and arterial stiffness e.g. carotid/aortic intima media thickness (IMT) and flow-mediated dilation (FMD) as a measure of vascular endothelial function are currently the best available markers of future cardiovascular disease. Notably, reduction in CVD outcomes with improved HbA1c in recent years is lagging behind the reductions observed in retinopathy and renal disease. This may indicate the need to focus on other cardiovascular risk factors including lipid profiles, sodium intake and blood pressure, rather than just lowering of HbA1c to prevent CVD in children with diabetes.

Atherosclerosis begins in childhood and in some cases may even start before birth (Dr Watts). Low density lipoprotein (LDL) plays a key role in atherosclerosis, the level of certain LDLs have been shown to be predictors of incident coronary artery disease. Statins have been shown to reduce the risk of CVD, with the reduction in risk shown to be proportional to the reduction in LDL levels. Therefore, statins are clearly indicated in patients with T1D. The use of statins in children with T1D is not yet clear. Results of the AdDIT trial will help answer some questions regarding the use of statins in children with T1D, bearing in mind that this trial is measuring early markers of cardiovascular disease and is not a clinical outcomes endpoint trial. Questions regarding the

tolerance of side effects, concerns about potential neurocognitive effects and the use of hydrophilic or lipophilic statins and whether or not effective treatment could be episodic rather than life long remain unanswered.

We are what we eat

Dr Forbes provided insights that dietary AGE consumption contributes to complications associated with T2D. High AGE diets results in hyperfiltration, an early finding in diabetic nephropathy. This provides further evidence that highly processed foods, and cooking techniques (such as deep frying) which have high AGEs, should be avoided.

Using advanced sequencing techniques and bioinformatics, Dr Heintz-Buschart found that the exocrine signature from the pancreas is different in patients with T1D compared to controls. She concluded that the community phenotype of the gut microbiome in patients with T1D is different from controls with potential implications for the pathogenesis of T1D.

One may think that obesity is simply a result of poor eating habits and a sedentary lifestyle, but there is a strong genetic and biological component (Dr Proietti). Most individuals who lose weight gain it all back. Why do diets fail? Body weight is regulated in the hypothalamus with involvement of several hormones for weight regulation. To maintain weight loss, individuals need to be focused, constantly vigilant of everything they eat and exercise daily. If life gets chaotic or stress causes a loss of focus, weight gain will likely occur.

Cutting edge technology

The goal of diabetes management is to improve glycaemic control, reduce hypoglycaemia and improve quality of life for patients and families. The rapid technological advances in the past decade have improved clinical management, with a reduced risk of severe hypoglycaemia. Pumps in association with continuous glucose monitoring (CGM), the low glucose suspend pump and the predictive low glucose suspend pump have significantly reduced overnight hypoglycaemia (Dr Jones), but also improved blood glucose variability.

However, there are three main components to any closed-loop system: a glucose sensor, a mechanism of insulin (and/or glucagon) delivery and the algorithm controlling the pump. Each aspect of the closed loop system has its own limitations - the accuracy of the sensors, dermatologic complications, algorithms controlling insulin delivery, biologic variability of the insulin action and meal absorption. Overnight closed loop studies, inpatient studies, hotel or diabetes camp studies and recently home studies have been completed with “hybrid” closed loop models, requiring a manual bolus entry for meals. Significant barriers to the complete closed loop system remain - most significantly is the time delay from food absorption, sensor detection and insulin delivery (Dr. Buckingham).

New drugs in Diabetes

SGLT2 inhibitors are an important new tool for the management of diabetes. Dr Cherney highlighted that the benefits are beyond glycaemia, particularly by minimising hyperfiltration to prevent early diabetic nephropathy. SGLT2 inhibitors have been shown to improve mortality from CVD in T2D. In T1D, SLGT2 inhibitors confer lowered HbA1c, lower fasting glucose, less hypoglycaemia, and a lower requirement for insulin.

GLP1 agonists are well established in the treatment of adult T2D. While there are many examples of GLP1 agonists, Dr Horowitz presented evidence that the affect on delaying gastric emptying favours short acting GLP1 agonists. In combination with basal insulin, there is added therapeutic advantage.
In a rapidly developing field, new insulin technology may herald a potential revolution in diabetes management. Smart insulins, using polymer based nanotechnology that act as glucose sensors were described by Dr Cohen. While studies are currently limited to animal data, preliminary results show promise, and this remains a much anticipated potential therapeutic.

Protecting mental health in Diabetes
The occurrence of depression and depressive symptoms in youth with T1D, as well as current standards and experiences with screening for these symptoms was reported by Dr Grey. The majority of research is based on depressive symptoms identified by validated screening, rather than formal diagnosis of clinical depression according to DSM criteria. Screening for depressive symptoms is recommended from age 10, which needs to be supported by appropriate referral pathways to mental health professionals. Barriers to screening are noted to include determining who is qualified to undertake screening, reluctance to screen due to family and professional concerns regarding stigma and burden, and difficulties in obtaining funding for both screening and adequate follow up. Depression carries with it suicide risk, and suicidal ideation and attempt in youth with diabetes is approximately double that of non-diabetic controls. Furthermore, depression is associated with poorer metabolic control, poorer quality of life, and greater rates of family conflict. A preventive approach with psycho-education through different formats addressing coping skills training early in the course of diabetes may be helpful in preventing escalation of symptoms and subsequent morbidity. Treatment options for comorbid depression include cognitive behavioural therapy, behavioural family systems therapy, and antidepressant medications.
Psychiatric disorders affect a large proportion of youth with childhood onset T1D (Cooper). Deidentified records from the Western Australian Childhood Diabetes Database was linked to the WA mental health information system, recording hospitalisations and community-based psychiatric services. The hazards ratio (HR) for any psychiatric disorder was 2.3 in those with childhood-onset T1D; the highest risk for eating disorders (HR 5.1). Increase in HbA1c was associated with an increased risk of affective disorders, anxiety and adult personality and behavioural disorders, but not for eating disorders or substance dependency.
On addressing the question of whether fear of hypoglycaemia is a mental health problem in pediatric T1D, Dr Gonder-Frederick gave the concise answer of “a very definite sometimes”. While some fear of hypoglycaemia can be a positive adaptive response to recognising a real danger of hypoglycaemia, when the level of concern does not match with level of risk problems arise, leading to inappropriate levels of worry, or alternatively inadequate concern and recognition of danger involved. Fear of hypoglycaemia (rather than severe hypoglycaemia itself) is associated with decreased quality of life. Fear of hypoglycaemia in children and youth has been associated with negative effects on glycaemic control, with higher average HbA1c, and fear of hypos can impact the mental health in parents of children with T1D. Improvements in pump technology with sensor-augmented pumps with predictive low glucose suspend may reduce frequency of

hypoglycaemia and provide reassurance, though these devices are not currently available or accessible to all families. While popular, the use of diabetes alert dogs have very little objective data to support their ability to accurately predict hypoglycaemic episodes.
However, the incidence of severe hypoglycaemia was reported decreasing according to data from the Norwegian Childhood Diabetes Registry, consistent with results from other centres. From 2001-2013 the rates of severe hypoglycaemia have decreased from 14.4 to 4.2 per 100 patient-years, with no significant change in HbA1c over the same time period.

Rights of Individuals with Diabetes

The first presentation focussed on the rights of the child with diabetes from an international perspective with a focus in resource poor communities. Dr Armstrong provided an overview of the UN Convention on the rights of the child and emphasised the need for international collaboration to promote the rights of children. Children are not to be viewed as powerless objects of charity but as human beings with rights. Communities and nations can be empowered through social media, partnerships and international collaborations.
Dr Stupiansky conveyed that diabetes and adolescence do mix. Adolescence has been referred to as a "culture bound syndrome", a developmentally unique period. Adolescence with diabetes is then viewed as being at an intersection of socially construed disease with actual biological disease. However, adolescence is the transitional period to adulthood with rapid identity formation along with physical, social and cognitive changes, though the common connotation is that it is a period of reckless and mindless risk taking behaviour. Moderation is the key and harm can be reduced by controlled experimentation. Technology can be used as an important secret weapon which can aid them in the decision making. Parents should be encouraged to give up control and transfer responsibility to the teenager over a period of time.
Dr McDowell shared the parallels in the complexity of care with disability and diabetes. The long-term goal is more than just minimisation of disorder-related harm but includes optimisation and adjustment of each individual at various stages in life. Identification of the child's supportive surroundings, access to information and empowerment along with medications help in achieving optimal long term goals.

Diabetes in Indigenous People

The burden of diabetes in Indigenous Australians is enormous and the gap between Indigenous and non-Indigenous Australians unacceptably large (Dr Brown). Indigenous Australians with diabetes are nine times more likely to die from CVD compared to their non-Indigenous counterparts. The gap between Indigenous and non-Indigenous Australians is likely to increase further as modern day health benefits to health in Indigenous Australians is not keeping track with the rest of the population. Key issues relate to disparities in access to healthy food and health services, socioeconomic burdens, and the downstream effects of a displaced population treated with a Western understanding of disease processes and rather than an Indigenous perspective of the same.

What is causing the increased incidence of T2D in these children (Dr Sellers)? Genetic factors including ethnicity and family history of diabetes play a role, and epigenetic factors related to

exposures in utero may also be important, together with obesity and low physical activity. Social factors, including chronic stress, poverty and low socioeconomic status also need to be addressed as related factors. Another key issue facing Indigenous people is that diabetes is a multigenerational disease and in many families, a child diagnosed with T2D may also have parents and grandparents affected by the disease with chronic complications such as end stage renal disease, and therefore are in a family environment where the care they require for their own diabetes cannot be provided.

Prenatal and antenatal strategies are aimed at improving early diagnosis and treatment of T2D, reducing access to sugary drinks and improving access to fruit and vegetables, as well as providing midwifery training about diabetes management. Postnatal strategies are focussed on improving breast feeding rates. It is hoped that this multi-pronged approach will help to reduce the burden of T2D in this population.

A potpourri of Highlights from Oral Sessions

Mentionable are the twin talks on MRI and brain function lead by Drs) Northam and Messazos) assessing altered glycaemic states on working memory, the effects of hypo and hyper glycaemia. Such MRI based functional analysis is world leading and opens up a Pandora's box of questions and clinical importance of "normo-glycaemia".

The third world presentation of insulin storage in "clay-pots" by Dr Ogle on behalf of Life for a Child, and the impressive bringing together of local material for insulin storage with some up to date science to assess the benefits was inspiring.

The clustering of high risk genotypes with co-occurrence of T1D and coeliac disease was highlighted. Individuals carrying high risk genotypes DR3-DQ2/DR3-DQ2 or DR3-DQ2/DR4-DQ8 are more likely to develop both autoimmune diseases.

HNF1 beta transcription mutations affected the expression of 4 microRNA (24, 223, 27D and 119A) levels in patients with HNF1-beta MODY (Dr Fendler). The downregulation of these microRNAs may be responsible for upregulation of pathways causing insulin resistance.

A snapshot of data from the Australasian Diabetes Data Network (ADDN) reported that fewer than half of the participants are meeting the ISPAD target of <7.5%. Children aged <= 6 had the highest BMI-SDS and across all groups, 39% were overweight or obese. The median HbA1c for ADDN patients under 15 is 8.1% which is higher than values reported for Germany, Austria and Sweden but lower than those for the UK and US.

The 42nd Annual ISPAD meeting will take place in Valencia, Spain from October 26-29, 2016. Details can be found at http://www.ispad.org/ . ISPAD and the organizing committee welcome the international pediatric diabetes community to attend.