ISPAD + APEG 2015

INVITED SPEAKERS' SESSIONS

Plenary Session I Robert Vines Lecture: Can We Put The Brakes On The Drivers Of Diabetes?

INV1

Burden, presentation and course of pediatric diabetes – lessons from SEARCH

D. Dabelea

University of Colorado Denver, Colorado School of Public Health, Aurora, USA

SEARCH for Diabetes in Youth is an on-going, culturally diverse, multi-center and population-based epidemiological study of youth with diabetes. Initiated in 2000 and encompassing the major racial/ethnic groups in the U.S., SEARCH was designed to estimate the prevalence, incidence and clinical presentation of diabetes in youth age <20 years, by age, sex, race/ethnicity and diabetes type. Over the last 15 years SEARCH has made important contributions to the field of pediatric diabetes, including:

(1). Establishing the increasing burden of both type 1 (T1D) and type 2 diabetes (T2D) among U.S. youth. SEARCH has recently shown that between 2001 and 2009 the prevalence of T1D in youth increased by 21.1%, and the prevalence of T2D increased by 30.5%. Projections suggest that, by 2050, the number of youth with T1D age <20 years will increase in the U.S. more than threefold, with the highest relative increase among minority youth, and numbers of youth with T2D will quadruple.
(2). Proposing a simple etiologic classification of diabetes type. SEARCH operationalized definitions of two main etiologic markers of diabetes, autoimmunity and insulin sensitivity, to identify four etiologic subgroups based on the presence or absence of markers.
(3). Determining that many youth with diabetes are at risk for acute and subclinical chronic complications, with the greatest risk in racial/ethnic minorities and those with T2D.
(4). Observing that, while many youth with diabetes are receiving quality care, a significant proportion of minority youth and "emerging adults" are not.

Diabetes presents a significant burden to the health of U.S. youth and represents a major clinical and public health challenge. SEARCH findings suggest that a substantial number of such youth will develop debilitating complications early in life, adversely affecting their quality of life and life expectancy.

INV2

Early tight control: Is it necessary and how can it be achieved?

E. Örtqvist

Karolinska Universitets, Pediatric Diabetes Unit, Stockholm, Sweden

To live with, and treat, insulin-dependent diabetes is a challenging task for children, teenagers and their families. Since it is well established that good long-term glycemic control, most often measured as HbA1c, is of central importance for both daily quality of life, and for the future prognosis regarding vascular and nerve complications, everyone involved in diabetes care seek means to help patients achieve this goal. Glycemic control during the childhood years of diabetes predicts outcome in adult age, as shown by following young persons with type 1 diabetes longitudinally from childhood to adulthood through the Swedish diabetes registers NDR and SWEDIABKIDS. Data will be presented from SWEDIAB-KIDS, a register to which all pediatric diabetes clinics in Sweden report, showing that good glycemic control already from diagnosis is achievable, and more importantly, leads to lower long-term HbA1c. The mean HbA1c-level in patients below 18 years of age decreased continuously for the last 5 years in Sweden from 63 to 58 mmol/mol (7.9–7.5%). Mean HbA1c for children below the age of 9 was stable around 53 mmol/mol (7.0%) in 2014, but thereafter increased unceasingly to a mean HbA1c of 63 mmol/mol (7.9%) in the 17 year old age group. Puberty and young adult age does not fit well with the diabetes self-care hassles, but also these age groups benefit greatly from an active approach to achieve well-balanced glucose values from diagnosis. The concept of "glycemic memory" will be discussed during this session, as well as other drivers of metabolic long-term control.

Intensive diabetes treatment involves several more features than the more apparent use of new technical diabetes devices such as advanced insulin pumps and CGM. Different aspects of successful strategies on a national, clinic/diabetes team-based and individual level will be presented and discussed, as well as difficulties and pitfalls facing the striving patients/families and diabetes teams.

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Symposium - Diabetes Session I Macrovascular Disease in Diabetes in the Young

INV3
Can we intervene earlier?

J. Couper[a,b], J. Anderson[a,b] & A. Pena[a,b]

[a]*University of Adelaide, Adelaide, Australia;* [b]*Womens and Childrens Hospital, Adelaide, Australia*

Cardiovascular disease remains the leading cause of mortality in type 1 diabetes (T1D) and vascular complications begin in childhood and adolescence. The DCCT and EDIC follow up continues to show that glucose control is the principal modifiable risk factor in the prevention and delay of macrovascular complications. However patients with T1D and HbA1c ≤6.9% still have over double the risk of all over mortality and almost three times the risk for cardiovascular causes of death as matched controls. Therefore to prevent macrovascular complications developing from childhood we must both improve glycaemic control and understand the modifiable non-glycaemic determinants.

Non glycaemic factors that may be important and impact the epigenome, as well as glycaemic control, are overweight/obesity (1/3 of adolescents with T1D in Australia are overweight), gender, smoking, residual C peptide, and unidentified gene environment interactions. The majority of adults with long duration T1D have detectable residual C peptide using sensitive methods, which is an independent protective factor for vascular complications. Female gender increases risk of cardiovascular disease in T1D relative to being male but whether this gender disparity in cardiovascular risk begins from adolescence or is explained by modifiable factors is not known.

The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) has examined surrogate markers of macrovascular disease at baseline to detect a relationship with both traditional cardiovascular risk factors and urinary albumin excretion, which maybe a biomarker of all vascular complications in T1D. As a consequence of the global obesity epidemic, increasing numbers of patients with T1D also are overweight and insulin resistant. The first trial to examine the effect of metformin on vascular function and structure in adolescents (Adelaide Metformin Trial) will also be presented.

INV3bis
Strategies to address the challenges of youth-onset type 2 diabetes among Aboriginal and Torres Strait Islander communities

L. Maple-Brown[a,b]

[a]*Menzies School of Health Research, Winnellie, Australia;* [b]*Royal Darwin Hospital, Division of Medicine, Tiwi, Australia*

Rates of type 2 diabetes among Indigenous Australian youth are greater than among non-Indigenous youth and appear to be rising. Indigenous youth with diabetes are more likely to be female, are frequently (but not always) obese, and experience complications of diabetes at a relatively young age. Challenges as a health care provider for this high risk population include addressing the social determinants of health, psycho-social stressors, issues of remoteness and limited resources. Strategies to address the emerging epidemic of type 2 diabetes among Indigenous youth need to commence as early as possible in the life-course. Opportunities to address the intergenerational nature of type 2 diabetes among Aboriginal and Torres Strait Islander communities include improving maternal health preconception and between pregnancies, particularly among young women with Type 2 diabetes themselves, optimising antenatal care, supporting breastfeeding and other early nutritional interventions.

INV4
Statins for all diabetic patients: the lower and the earlier the better?

G.F. Watts

School of Medicine and Pharmacology, Lipid Disorders Clinic, Royal Perth Hospital, University of Western Australia, Cardiovascular Medicine, Perth, Australia

Statins are proven and safe therapies for preventing and reversing atherosclerotic cardiovascular (CVD). Statins achieve this by principally lowering the plasma concentration of LDL particles and as a consequence by improving endothelial function, arterial inflammation and stabilizing high risk plaques in the arterial wall.

The causal and temporal role of low density lipoprotein-cholesterol (LDL-C) in CVD has recently been well attested by Mendelian randomization studies. Genetically lower LDL-C (i.e. from birth) has a far greater impact on CVD outcomes than the lowering of LDL-C in short-term (2–5 year), large clinical endpoint trials.

This implies that very high risk individuals with chronic conditions should be identified and treated at an early stage in life. High risk subjects can include those with diabetes and inherited high cholesterol. In diabetes, quantitative and qualitative abnormalities in LDL particles and the arterial wall are major drivers of CVD. Other drivers of risk are age, hypertension, renal insufficiency, smoking, obesity and adverse family history of CVD.

The proposition that all diabetic people should be treated with a statin as early as possible needs to be understood in the way it can be true in real life. Hence, the proposition is true contingent on the circumstances in which the use of statins are justified by trial evidence, expert opinion or good clinical judgement.

Hence, statins should be used in all young diabetic patients with established CVD and in those without CVD who have an LDL-C >4.1 mmol/l or >3.4 mmol/l in presence of other CVD risk factors, including those referred to above. Clearly, there should be no contraindications to using a statin, the patient should be fully informed, and the decision to treat should be individualised and revised with appropriate clinical monitoring.

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Symposium - Diabetes Session II "Mythbusters" in Diabetes

INV4bis

It is easy to lose weight. . .

J. Proietto

University of Melbourne, Department of Medicine, Heidelberg, Australia

It is easy to lose weight but almost impossible to keep it off. There is clear evidence that most individuals regain the weight that they have lost through diet and lifestyle change. Those that maintain the weight have to be very mindful of everything they eat and make an effort to exercise daily. Why is weight maintenance a struggle? To understand this is necessary to briefly review the biology of body weight regulation. Body weight is controlled by the hypothalamus. Within the arcuate nucleus of the hypothalamus are two classes of nerves, the NPY nerves that also produce and secrete hunger producing AGRP and the POMC nerves that secrete CART and MSH which inhibit hunger. These "first order neurons project to other areas of the hypothalamus which then produce the desire to eat or not. The firing of these first order neurons is in turn controlled by circulating signals originating in the gut, in fat and in the pancreas. There are many hunger controlling hormones. One, Ghrelin, is made by the stomach and stimulates hunger. The others, CCK, PYY, GLP-1, oxyntomodulin, uroguanilin from the small bowel, leptin from fat and insulin, amylin and pancreatic polypeptide from the pancreatic islets, all inhibit hunger. Soon after the discovery of leptin and ghrelin it was discovered that following weight loss, leptin levels fall while ghrelin levels rise, both changes leading to increased hunger. In 2011 we showed that the levels of other circulating hormones also change in a direction to induce hunger and that these changes are long lasting (1,2). In addition weight loss induces a reduction in energy expenditure of ~300 kcal that is also long lasting. Hence the weight reduced individual has to battle hunger while being more fuel efficient.

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Symposium - Endocrine Session I Specialised Endocrinology Aftercare of Childhood Cancer Survivors

INV5
Long term metabolic sequelae of childhood cancer and its treatment

K.A. Neville[a,b]

[a]*Sydney Children's Hospital, Endocrinology, Sydney, Australia;* [b]*University of New South Wales, School of Women's and Children's Health, Sydney, Australia*

Advances in the care of children and adolescents diagnosed with cancer have resulted in over 80% long-term survivorship. Approximately 70% of childhood cancer survivors (CCS) however will develop at least one medical sequelae of their treatment by 30 years from diagnosis, with endocrine sequelae affecting between 20–50% of individuals. Metabolic sequelae, including insulin resistance and type 2 diabetes mellitus, obesity, dyslipidaemia and hypertension are being increasingly recognised in a number of survivor populations, but exact rates and risk groups are difficult to characterise because of the use of variable definitions within the literature. Those exposed to total body, cranial and abdominal irradiation appear to be at greatest risk, but a multitude of factors including bone marrow transplantation, alkylating agents, corticosteroid use, any hormonal deficiencies, reduced physical exercise, alterations in gut microbiota and genetics have been variably invoked. CCS are 7 times more likely to die from cardiovascular disease than the general population of similar age, highlighting the importance of identifying evidence-based interventions that minimise metabolic complications, taking into account the unique limitations of this population including physical disabilities and disease fatigue. This symposium will provide a general overview of the metabolic abnormalities faced by survivors of childhood cancer, explore populations at particular risk and physiological lessons learnt from these groups, with a review of recent data supporting the role of physical exercise and dietary habits of CCS in the development of these complications.

INV6
Skeletal health in survivors of childhood cancer

C.F. Munns[a,b]

[a]*The Children's Hospital at Westmead, Endocrinology and Diabetes, Westmead, Australia;* [b]*University of Sydney, Medical School, Sydney, Australia*

Osteoporosis with pathological fracture and osteonecrosis (ON) are two significant complications of childhood cancer with morbidity that can last well into adult life.

Vertebral compression fractures are a frequent complication of acute lymphoblastic leukaemia (ALL) with up to 16% of children developing an incident compression fracture during the first 12 months of treatment. Of this with an incident fracture, over 50% had a vertebral fracture at baseline. Osteoporosis during treatment of ALL/lymphoma has been reported with bisphosphonates being shown to increase bone density. There are a paucity of longitual data on fracture incidence in survivors of childhood cancer. Available cross-sectional data would indicate that fracture rate is not increased compared to sibling or population controls.

ON is a disabling complication of chemotherapy for ALL and lymphoma, especially steroids in children and adolescents. It can affect multiple joint but is most commonly seen in the knees and hips. The reported incidence is between 5–30% and varies depending on the screening method used. Glucocorticoid use is the major risk factor, but other risk factors include age >9 years, female sex, Caucasian race and high body mass index. Other medications may modify risk as may specific genotypes. The management of ON is primarily symptomatic. Bisphosphonate therapy has been shown to be ineffective in preventing hip collapse, but may be of benefit for children with knee ON. Joint replacement is frequently required in the second to third decade of life for those with significant pain from joint collapse. Preventative trials are currently underway.

This talk will cover the aetiology, incidence and management of osteoporosis and On in children with cancer, specifically ALL and lymphoma.

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Plenary Session II Diabetes In Indigenous Peoples

INV7
Type 2 diabetes in Indigenous children

E.A. Sellers[a,b]

[a]*University of Manitoba, Pediatrics and Child Health, Winnipeg, Canada;* [b]*Children's Hospital Research Institute of Manitoba, Winnipeg, Canada*

Historically, type 2 diabetes has been considered a disease of adults. However, over the past several decades the incidence and prevalence of type 2 diabetes in children (onset <18 years of age) has increased worldwide, disproportionally effecting children of Indigenous origin. In this presentation, topics of discussion will include: (1) the epidemiology of type 2 diabetes in pediatric Indigenous populations, (2) our current understanding of the increased burden in Indigenous children, (3) a discussion of barriers to prevention and care and (4) emerging outcome data in this vulnerable population.

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Clinical Practice Symposium - Diabetes Session I Teams, Teamwork and Targets

INV8
The way to the optimal multidisciplinary team. A Danish perspective

B.S. Olsen

Herlev University Hospital, Department of Pediatrics, Herlev, Costa Rica

Over the last 10 years the Herlev Paediatric Diabetes Clinic, Copenhagen, has undergone major changes, including a doubling of patients from 280 to 545. In the same period there has been major changes in insulin treatment regimens, including a shift from the majority of patients having pre-mixed insulin two times daily to widespread use of CSII and CGM.

This change has required expansion, ongoing education and coaching of the team, as well as and the development of advanced patient and family educational programs.

This together with our 24-h telephone hotline, have resulted in improved metabolic outcome. Presently mean Hba1c of our patients is 61 mmol/mol and more than 45% obtain the goal of HbA1c <58 mmol/mol. Simultaneously we have reduced our frequency of severe hypoglycaemia to 2 per 100 treatment years.

Together with the Steno Diabetes Centre we have developed a well-structured transition program for our young patients. The program has shown promising results as HbA1c is not increasing after the transition, all patients are screened for complications and no patients are lost in transition.

We have a research oriented environment and have ongoing research in basic as well as clinical fields. An important instrument for data collection is the Danish Registry for Diabetes in Childhood (DanDiabKids), containing data on all Danish children with diabetes in Denmark. The registry has also proved to be an excellent tool for benchmarking, both nationally and internationally.

INV9
How teamwork improves patient outcomes: implications for clinical practice

B.R. King[a,b,c]

[a]*John Hunter Children's Hospital, Department of Paediatric Diabetes and Endocrinology, Newcastle, Australia;* [b]*University of Newcastle, Hunter Medical Research Institute, Newcastle, Australia;* [c]*University of Newcastle, Hunter New England Diabetes Research Network, Newcastle, Australia*

The introduction of analogue insulins and intensive insulin regimes promised improved glycaemic control for people with type 1 diabetes. However, the Hvidoere International Study Group (HISG) found no evidence of improved glycaemic control with the introduction of these new methods. The HISG demonstrated a wide variability of glycaemic outcomes across different centres. The main association with good outcomes was the team, the patient and the family having a consistent glycaemic target. This suggests that the communication within the team and with the patient and family may have a significantly influence patient outcomes. The HISG found no association between the make-up of the team or the staff: patient ratio. This suggests that it is the way the team works together with the patient and the family that is important in patient outcomes.

Education theories state that learning and implementation is improved if the messages/information are repeated, consistent, understandable and come from a reliable source. Additionally, an element of peer pressure assists to convey the message. Teamwork means that the individual team members work together to deliver information that is accurate, consistent, understandable and most importantly reinforces/adds to information given by other team members.

When teamwork is absent, messages may be inconsistent, contradictory or fragmented and the patient/family will have difficulties utilizing the information to develop a management plan.

This talk will focus on strategies to improve teamwork including team development of written messages, philosophies, goals, targets, and team communication strategies. The need for collaboration, openness, respect, empowerment and pragmatism will also be highlighted. The impact of these strategies on patient outcomes will be discussed.

INV10
How to manage and promote teamwork when resources are limited

V. Bhatia

Sanjay Gandhi Postgraduate Institute of Medical Sciences, Endocrinology, Lucknow, India

The multidisciplinary diabetes education team is recognised as the centrepiece of successful diabetes management programs. However, the mere availability of a team, or the absence of economic constraints, do not necessarily ensure good outcome. Disparities exist in developed countries too, due to barriers to care, both access and process barriers, including costs, communication and access to information. Barriers are perceived by low socioeconomic groups, and also by ethnic or linguistic minorities, and families with low parental educational status. Contextualised care, taking into account the patient's personal and family context, and allowing for evaluation of the program by the patient/family, has been shown to make diabetes education and care more meaningful. Motivational interviewing of the teenager with diabetes has produced tangible results in diabetes outcomes. Imparting such skills to the primary care paediatrician and adopting a pragmatic design of care delivery may ensure sustainability in limited resource settings.

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Symposium - Endocrine Session III -Norman Wettenhall Symposium: Growth: from Genes to Growth Hormone

INV11
Woolie tales of obesity

I. Clarke & B. Henry

Monash University, Physiology, Melbourne, Australia

Obesity is a complex condition that can be caused by psychological conditions, simple overeating, lack of exercise, epigenetics and genomic factors. We have studied innate factors that predispose to an obese phenotype, using sheep as a model. Genetic selection for lean or 'obese' phenotype provided us with an opportunity to study factors that are genetically imprinted. We found that the expression of genes encoding appetite regulating factors in the brain were different in the two selected lines. Although the lean and fat animals have equivalent voluntary food intake, there are differences in energy expenditure, specifically thermogenesis, that account for their differing body composition.

In a second series of studies, we selected animals from an outbred population that had either high or low cortisol responses to a Synacthen (adrenocorticotropin) challenge. High responders (HR) had a greater propensity to become obese on a high energy diet than low responders (LR). Adaptive thermogenesis in muscle was greater in LR, explaining their lean phenotype. These two groups of animals also display differences in the expression of genes throughout the hypothalamo-pituitary-adrenal axis and different response to specific stressors. In addition, LR animals were more active and had a proactive behavioural phenotype, whereas HR animals were reactive in nature. The cortisol responsiveness to Synacthen is maternally inherited. These innate, heritable phenotypic differences provide markers that can be used to identify individuals with greater or lesser likelihood of becoming obese on high energy diets.

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Symposium - Diabetes Session III - New Drugs in Diabetes

INV12
Sodium glucose cotransport-2 inhibition and the potential for renal protection in diabetic nephropathy

D. Cherney

University Health Network, University of Toronto, Medicine, Division of Nephrology, Toronto, Canada

Early type 1 diabetes is characterized physiologically by a state of increased intraglomerular pressure, leading to renal hyperfiltration in patients with diabetes mellitus. Unfortunately, current therapies that block the renin angiotensin aldosterone system do not completely attenuate hyperfiltration or diabetic kidney injury. More recent work has therefore investigated the contribution of renal tubular factors, including sodium glucose cotransport, to the hyperfiltration state.

Sodium glucose cotransport-2 (SGLT2) inhibitors reduce proximal renal tubular sodium reabsorption, thereby increasing distal sodium delivery to the macula densa. This natriuretic effect increases tubuloglomerular feedback, leading to afferent vasoconstriction and decreased hyperfiltration in animals, and also reduces hyperfiltration in normotensive, normoalbuminuric patients with type 1 diabetes. In clinical trials involving patients with type 2 diabetes, SGLT2 inhibition is associated with modest, acute and reversible declines in eGFR and reduced albuminuria, followed by maintenance of stable renal function. Similar to experimental animal models and mechanistic data in humans, SGLT2 inhibition effects in glycemic control trials may therefore reflect the impact of this new class of drugs on renal hemodynamic function.

In addition to effects on glycemic control, weight and blood pressure, SGLT2 inhibition influences renal hemodynamic function and may reduce intraglomerular hypertension and albuminuria. Dedicated renal outcome trials are underway and have the potential to change clinical practice.

INV13
New and smart insulins

N. Cohen

BakerIDI Heart and Diabetes Institute, Melbourne, Australia

Insulin therapy is the cornerstone of the management of type 1 and complex type 2 diabetes. It is now over 30 years since the introduction of human insulin, and insulin analogues have become increasingly important in modern management, resulting in greater flexibility and lower risk of hypoglycaemia. There are a number of new insulin preparations on the horizon which may provide further improvements for patients. These include longer acting basal analogues, faster rapid analogues, oral insulin and smart insulin. Many of these new preparations have the potential to change outcomes and quality of life for patients with diabetes.

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Clinical Practice Symposium - Diabetes Session II The Challenges of Toddlers with Diabetes

INV14
The medical management of infant and toddler diabetes

D. Cody

Our Lady's Children's Hospital, Crumlin, Dublin, Ireland

The rising incidence of type 1 diabetes, particularly in the young preschool child, has significant implications for both parents and health professionals. Infants and toddlers have various age-related clinical and psychosocial characteristics, making the management of their diabetes distinct from that of older children.

At initial presentation very young children have a notable increase in the risk of diabetic ketoacidosis and cerebral oedema compared to older children. They have higher titers of diabetes-related autoantibodies indicating a more aggressive autoimmune insult.

Both daily activity and food intake can be variable. Food intake patterns, including grazing and of course food refusal, are more common. Younger children tend to be more prone to infections. Variable blood sugar patterns with unpredictable fluctuations are part of the management difficulties. Significant concerns regarding hypoglycaemia, especially nocturnal, are common for parents in this age group.

These clinical and psychosocial issues often mean that both parents and health professionals can struggle with ensuring good clinical control while minimizing family stresses. The pre-pubertal protection from complications is now readily disputed, reinforcing the need for good early glycaemic control. Providing more physiological insulin regimens should be strongly advocated and insulin pump therapy is ideally suited to this age group for suitable families.

The importance of a specialized multi-disciplinary team in providing on-going education and close support to families of very young children with diabetes is an essential component of an effective children's diabetes service. It is important that diabetes team members are experienced in managing diabetes in this age group and a hub and spoke model between regional and smaller centres, if required, should be encouraged for the younger child with T1D.

INV15
Overcoming the challenges in the nutritional management of toddlers with diabetes

S. Youde

Royal North Shore Hospital, The Department of Paediatric Diabetes and Endocrinology, Sydney, Australia

All toddlers are individuals with different personalities. They will all develop, physically and emotionally, at differing rates. It's the same for all toddlers with diabetes, but having diabetes presents some additional management challenges in this rapid stage of human development.

From a physiological perspective research indicates that young children with type 1 diabetes are often highly insulin sensitive, potentially complicating the regulation of blood glucose levels (1).

Some research suggests that toddlers with type 1 diabetes often demonstrate increased independence seeking, transient food preferences, behavioural resistance, and volatile emotions, which can affect adherence to treatment (2). Parents of toddlers and young children frequently report problems with mealtimes and adherence to guidelines for carbohydrate intake (2) and studies have found associations between poor parent-child mealtime behaviours and poor dietary adherence and glycaemic control (3).

The presentation will explore the particular nutritional challenges, evidence based practice and practical strategies to help families navigate this challenging phase.

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INV16
Parenting a toddler with diabetes

J. Ivancsik

The Children's Hospital at Westmead, Institute of Endocrinology and Diabetes, Westmead, Australia

Healthcare professionals play an important role in shaping the way parents think about their child with diabetes. This presentation will integrate current literature, clinical practice wisdom and caregivers' experiences to explore the impact of parenting on health outcomes and psychological adjustment to diabetes.

Research suggests that the diagnosis of diabetes is a crucial variable that influences parent's psychological wellbeing and their ability to parent. Due to the pace of growth in infancy and toddlerhood (0–3 year olds), children have more rapid changes in development and behaviour than at any other stage of childhood. Therefore the treatment and management of diabetes in infants and toddlers pose unique challenges for their caregivers and healthcare professionals alike.

Post the diagnosis of diabetes parents are faced with the complex task of balancing competing needs and demands to achieve optimal glycaemic control and quality of life for their child. Carers of toddlers often struggle to adjust their parenting approach to keep normality in their child's life in a way that promotes positive physical, cognitive and emotional development, while integrating the day-to-day management of diabetes. Parents of toddlers with diabetes report higher parenting stress as well as higher levels of anxiety and fear associated with managing the condition, in particular fear of hypoglycaemia. These diabetes-specific worries and anxieties often lead to maladaptive coping strategies, such as over-protective parenting, which is shown to increase child-perceived vulnerability. This sense of vulnerability has been linked with an increased risk of depression and anxiety later in life.

Social Work can provide early intervention and support for parents with a toddler with diabetes which may be the key to establishing a solid parental framework; this is created through parent education, counselling and a multidisciplinary approach.

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Plenary Session III Protecting Mental Health In Diabetes

INV17
Screening and prevention of depression in youth with type 1 diabetes

M. Grey

Yale University, School of Nursing, Orange, United States

Youth with Type 1 diabetes have a substantial risk of dealing with depressive symptoms, and in some cases, treatable depression. In this talk, I will review the literature on screening for depression. In addition, examples of early intervention programs and treatment programs will be provided. Implications for practice in these vulnerable youth will be discussed.

INV18
Fear of hypoglycemia in pediatric type 1 diabetes: global findings and clinical implications

L. Gonder-Frederick

Behavioral Medicine Center, University of Virginia, Charlottesville, United States

Research using the Hypoglycemia Fear Survey (HFS) has demonstrated that youth with type 1 diabetes and their parents typically experience some level of fear of hypoglycemia (FoH), which is not surprising given the potential negative consequences of low blood glucose levels. Indeed, parents of type 1 youth often exhibit higher levels of FoH than adults living with type 1 diabetes. Extreme levels of FoH can have a negative impact on emotional well-being which is associated with a decrease in quality of life, and on diabetes management which is associated with problems in glycemic control. This presentation will review findings on FoH in pediatric type 1 diabetes from several diverse countries and cultures, including Turkey, Iran, Australia, Norway and the United States in order to begin to understand the problem of FoH from a global perspective. Risk factors that contribute to higher levels of FoH in both parents and youth will be reviewed, focusing on cultural differences and similarities. The clinical implications of FoH will also be reviewed, focusing on different types of interventions to reduce high levels of fear and anxiety, ranging from psychobehavioral programs to the use of glucose monitoring technologies. Current education, training and support programs for youth and parents living with type 1 diabetes do not adequately prepare families to cope with the emotional and behavioral impact of hypoglycemia and a concerted global effort is needed to address this problem.

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Clinical Practice Symposium - Diabetes Session III Meet the Experts: Difficult Clinical Cases

INV19
Sick day management in diabetes – Bangladesh perspective

B. Zabeen

Bangladesh Institute of Research and Rehabilitation of Diabetes, Endocrine and Metabolic Disorders, Paediatrics & CDiC, Dhaka, Bangladesh

It is well recognised that any acute illness may cause ketoacidosis, dehydration, uncontrolled hyperglycaemia and hypoglycaemia in a diabetic child. Initiation of early treatment may reduce the risk of severe hypoglycaemia or ketoacidosis and also the need for admission.

Sick day management is a one of the major challenge in managing children with diabetes in a developing country like Bangladesh. Though glucometer strips are available but it is unaffordable for most of our children. Ketone strip is not extensively available. Around 2000 children and adolescents are registered in our clinic in BIRDEM. Most of our children cannot afford to buy glucometer strips or acetone strips. Only 10% of our children in clinic can afford to buy glucometer strips on their own. We are providing only glucometer with few strips (10–30 strips/month) through our CDiC and LFAc programme in other children who are coming to our clinic. The diabetes care team provides clear guidance to patients and parents how to manage diabetes during illnesses. They emphasize on "insulin should not be stopped" during the education session. Children are provided the mobile phone numbers of the team so they can contact over phone when they become sick. Considering the lack of facilities of acetone strips they are advised to do CBG only and call the team while it is low (<4 mmol/l)or high (>15 mmol/l) and dose is adjusted according to the blood glucose level. During two months period in 2014, 40 children called the team, among them 10% had fever, 2.5% had vomiting and 2.5% had diarrhea. While analyzing the metabolic problems, we found that 15% developed hypoglycaemia whereas 10% developed hyperglycaemia and 2% required admission due to mild DKA. Despite all the constraints of acetone or glucometer strips, hospital admission could be avoided due to acute illness. The extensive use of mobile phone and intensive education by our diabetes team may contribute to reduction of hospital admission.

INV20
Sick day management in type 1 diabetes, challenges in the developed world

F. Mouat

Starship Children's Hospital, Paediatric Endocrinology and Diabetes, Auckland, New Zealand

The 2014 ISPAD Clinical Practice Consensus Guidelines state that children and teenagers whose diabetes is under good metabolic control should not experience more illness or infections than children without diabetes. However illness and stress are commonplace in the paediatric population, and in young people with T1DM the resulting counter regulatory hormone production can cause significant metabolic deterioration. This may lead to hyperglycaemia, ketonaemia and Diabetic Ketoacidosis (DKA). In this interactive session we will reference the guidelines and discuss some of the strategies and new technologies available to help prevent this potentially fatal condition. We will present cases to highlight the use of education and technology in promoting self-monitoring of blood glucose and ketones, thus allowing recognition of the early symptoms of hyperglycaemia and DKA. Approaches to the management of patients using insulin pump therapy will also be discussed and illustrated by case examples.

INV21
Eating disorders

P. Bergman[a] & H. d'Emden[b]

[a]*Monash Children's Hospital, Monash Health, Department of Paediatric Diabetes and Endocrinology, Melbourne, Australia;* [b]*Mater Health Service, Queensland Diabetes and Endocrine Centre, Brisbane, Australia*

Disordered eating and clinical eating disorders occur more frequently in adolescents and young adults with type 1 diabetes mellitus (T1DM) than their peers. Some reasons for this increase include a focus on food and weight with flexible insulin dosing, and the unique ability to use insulin manipulation or omission as a compensatory behaviour.

Disordered eating and clinical eating disorders may result in increased morbidity and mortality including impaired mental health, suicide, retinopathy, neuropathy and nephropathy.

Early detection of eating disorders and disordered eating is very important to potentially prevent the problem escalating. The use of validated screening tools which detect weight and shape concerns at any early stage, along with the associated behaviours allow for such early detection. Clinical markers can help but are often seen after the problems and behaviours are entrenched. Weight profiles can be unremarkable, HbA1c is usually elevated but not always, and there are often other possible reasons which contribute to the adolescent not taking adequate insulin.

At the time of screening for disordered eating, a comprehensive psychosocial assessment using other tools to identify factors such as depression, anxiety, diabetes burden and quality of life is recommended. If identified a full psychological assessment is warranted to ascertain the priorities of intervention.

Early stage disordered eating is best managed within a diabetes team, however the management is often time consuming, prolonged and intense so that, involvement of a specialist eating disorder team, or clinical psychologist within the diabetes team will often be necessary. The timing of referrals to such a team is often uncertain.

Awareness of possible disordered eating, actively screening for such problems and early intervention and expert management will lead to reduced morbidity and mortality of this very at risk group of young people.

INV22
Type 2 diabetes mellitus in childhood – a Singapore perspective

W. Lee[a,b]

[a]*Dr Warren Lee's Paediatrics, Growth & Diabetes Centre, Singapore, Singapore;* [b]*KK Womens and Children's Hospital, Singapore, Singapore*

A history of IUGR/SGA followed by rapid catchup growth and childhood obesity is a key predictor for diabetes in developing

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countries, while the typical Singaporean case is that of a middle class teen with a GDM mother and many T2DM relatives.

(1) Type 1 and Type 2 diabetes can coexist in the same extended family and some children may have features of both – the so called Type 1.5 diabetes or double diabetes

(2) Post-meal hypoglycemia is sometimes seen in T2DM and in prediabetic states due to a delayed insulin secretion, giving rise to an immediate postmeal hyperglycemia and then followed by hypoglycemia. A careful history or an extended OGTT with insulin may reveal this pattern (Hofeldt D, 1989).

(3) Insulin should be a first line therapy for children and adolescents with T2DM: in DKA, when Diagnosis is unclear, when presenting glucose is high >250 mg/dl, and when HbA1c is >9%. (4) In all other cases, Metformin should be the drug of first choice for T2DM in Kids (Copeland K. Pediatrics 2013; 131: 364–382). (5) The choice to use insulin or metformin in the adolescent T2DM patient is a dynamic decision, based on the patient's needs. Intercurrent Illness, exams, school projects and boy girl relationships can cause increases in insulin requirements, necessitating a switch between oral meds and insulin. As children grow into young adults, the choice of medications may then include the use of DPP4 inhibitors and SGLT2 inhibitors, as well as GLP-1 agonists. (6) Keep an open mind on the final diagnosis: The patient may have "high output failure" with insulin deficiency in the face of high serum insulin levels, ior "low output failure", necessitating early introduction of insulin. Slow onset Type 1 DM (LADA) and Monogenic diabetes may also present in the childhood and teenage years and it is important to clarify the diagnosis over time using an OGTT with concurrent insulin levels, GADAb, ICA, and celiac and thyroid antibodies ± gene testing for monogenic diabetes.

INV23
Type 2 diabetes in childhood – a Western Australian perspective

M. Shah

Princess Margaret Hospital for Children, Endocrinology and Diabetes, Perth, Australia

The diagnosis of a child or adolescent with type 2 diabetes remains relatively uncommon, but nonetheless a persistent and developing problem worldwide, the incidence of which increases at puberty with a corresponding higher female rate. A definitive diagnosis may not be clear initially, as there is a wide spectrum from an asymptomatic, opportunistic finding to the unwell child with severe hyperglycaemia and ketosis. It is unusual to see the presentation of a child aged <10 years, however in Western Australia, there have been several cases in recent years.

A case study of a female, aged 7 at diagnosis, from a remote community will be presented that highlights the key features often seen in these young children. Obesity (often severe) is usually evident but not always. This case will discuss some of the familial predictors of future health problems such as gestational or maternal diabetes, chronic disease and sometimes substance misuse. Social disadvantage and a dysfunctional family environment often lead to an unwell and delayed presentation. Co-morbidities such as hypertension, microalbuminuria and dyslipidaemia may also feature. Complex treatment used with the aim of optimal glycaemic control and to manage comorbid complications is usually required along with significant lifestyle changes, which is challenging in an often-chaotic family environment.

A key element in the case of this now 10-years-old girl and in many of these pre-pubertal presentations, is the child's vulnerability and the family's home life. The absence of adequate family and community support for this child led to non-adherence and suboptimal glycaemic control with exacerbation of diabetes complications. Conversely, improved care at home along with support from school and other external agencies has led to a thriving young girl with reversal of albuminuria and excellent glycaemic control.

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Symposium - Endocrine Session IV ESPE/ISPAD Symposium: Hypoglycaemia due to Endocrine Disorders

INV24
Hyperinsulinaemic hypoglycaemia

K. Hussain

Institute of Child Gealth, Endocrinology, London, UK

Insulin secretion from pancreatic β-cells is tightly regulated to keep fasting blood glucose concentrations within the normal range (3.5–5.5 mmol/l). Hyperinsulinaemic hypoglycaemia (HH) is a heterozygous condition in which insulin secretion becomes unregulated and its production persists despite low blood glucose levels. It is the most common cause of severe and persistent hypoglycaemia in neonates and children. The most severe and permanent forms are due to congenital hyperinsulinism (CHI). Recent advances in genetics have linked CHI to mutations in 9 genes that play a key role in regulating insulin secretion (*ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A and HNF1A*). Mutations in genes *ABCC8* (SUR1 subunit) and *KCNJ11* (Kir6.2 subunit) are the most common cause of CHI. Both the *ABCC8*/*KCNJ11* genes are localized on chromosome 11p15.1. The most severe forms of CHI are due to recessive inactivating (loss of function) mutations in *ABCC8* and *KCNJ11* leading to unregulated insulin secretion despite severe hypoglycaemia. Dominant inactivating mutations in *ABCC8* and *KCNJ11* usually cause a milder form of CHI which is responsive to diazoxide. However, medically un-responsive forms have also been reported.

Histologically, CHI can be divided into 3 types: diffuse, focal and atypical. Given the biochemical nature of HH (non-ketotic), a delay in the diagnosis and management can result in irreversible brain damage. Therefore it is essential to diagnose and treat HH promptly. Advances in molecular genetics, imaging methods (18F-DOPA PET-CT), medical therapy and surgical approach (laparoscopic surgery) have completely changed the management and improved the outcome of these children.

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Symposium - Diabetes Session IV Hot Topics in the Basic Science Arena

INV25
Coping with stress: IL-22 and cytokines in beta cell function

S.Z. Hasnain[a], D. Borg[b], F. Steyn[c], T. Huynh[d], B. Harcourt[b], H. Tong[b], Y. Sheng[b], C.P. Ng[b], I. Das[b], R. Wang[b], A.C.-H. Chen[b], T. Loudovaris[e], T.W. Kay[e], H. Thomas[e], J.P. Whitehead[b], J. Forbes[b], J. Prins[b] & M.A. McGuckin[b]

[a]*Mater Research Institute-University of Queensland, Mucosal Diseases, Brisbane, Australia;* [b]*Mater Research Institute-University of Queensland, Brisbane, Australia;* [c]*School of Biomedical Sciences, University of Queensland, St Lucia, Brisbane, Australia;* [d]*Endocrinology & Diabetes, Lady Cilento Children's Hospital, Brisbane, Australia;* [e]*St Vincent's Research Institute, Melbourne, Australia*

β-cell dysfunction in type 2 diabetes is accompanied by adverse cellular responses to high concentrations of lipids/glucose, oxidative stress, endoplasmic reticulum (ER) stress and local inflammation, although the relative contribution of these inter-related factors has remained unclear. Here we present the first evidence that a suite of cytokines, previously not identified as contributors to β-cell dysfunction, induce ER stress, thereby impairing insulin biosynthesis and secretion, whereas another cytokine, IL-22, suppresses ER stress and restores insulin production. The IL-22 receptor (IL-22R1) is most highly expressed by islet secretory cells and IL-22 directly acted to down-regulate pro-oxidant genes and up-regulates anti-oxidant genes in murine MIN6N8 β-cells and islets, and human islets. IL-22R1 neutralising antibodies induce oxidative/ER stress in healthy mouse and human islets, demonstrating that IL-22-IL-22R1 signalling maintains islet homeostasis. Islets from mice with high fat diet-induced obesity show immune activation, chronic ER stress and hypersecretion of insulin. *Ex-vivo* exposure to IL-22 suppresses ER stress and chemokine production, and reduces glucose-stimulated insulin secretion. Systemic administration of recombinant IL-22 to diabetic mice eliminated pancreatic ER stress and decreased pancreatic inflammation, while reversing β-cell abnormalities. IL-22 promoted high quality insulin production (decreased serum proinsulin by 92%), which restored glucose homeostasis without altering peripheral insulin sensitivity. However, after 4 weeks treatment serum proinsulin returned to normal levels and insulin sensitivity was restored. Taken together these data suggest that IL-22 is a natural regulator of β-cell insulin biosynthesis and secretion, protecting the β-cell from stress, preventing hypersecretion of poor quality insulin, and suppressing innate islet inflammation.

INV26
Programming of beta cell function for life: is it all over before birth?

R. Simmons

Perelman School of Medicine University of Pennsylvania, Pediatrics, Philadelphia, USA

The abnormal intrauterine milieu of intrauterine growth retardation (IUGR) permanently alters gene expression and function of pancreatic b-cells leading to diabetes in adulthood. Expression of the pancreatic homeobox transcription factor *Pdx1* is permanently reduced in IUGR and epigenetic modifications are responsible for this decrease. *Pdx1* encodes a homeobox transcription factor critically important for beta-cell function and development. The fetal IUGR state is characterized by loss of USF-1 binding at the proximal promoter of *Pdx1,* with deacetylation of histones H3 and H4 due to recruitment of the histone deacetylase HDAC1 and the co-repressor Sin3A. After birth, H3K4 is demethylated and H3K9 is methylated. During the neonatal period, the reduction in *Pdx1* expression and these epigenetic changes can be reversed by HDAC inhibition. Finally, once diabetes occurs, DNA methylation of the CpG-island in the proximal promoter ensues, resulting in permanent silencing of the *Pdx1* locus.

Using the HELP assay, we generated the first DNA methylation map of the rat genome in normal and IUGR ß-cells. We validated candidate dysregulated loci with quantitative assays of cytosine methylation and gene expression. IUGR changes cytosine methylation at 1,400 loci (in male rats at 7 weeks of age, preceding the development of diabetes and thus representing candidate loci for mediating the pathogenesis of metabolic disease that occurs later in life. Epigenetic dysregulation occurred preferentially at conserved intergenic sequences, frequently near genes regulating processes known to be abnormal in IUGR islets, such as vascularization, ß-cell proliferation, insulin secretion, and cell death, associated with concordant changes in mRNA expression. These results demonstrate that epigenetic dysregulation is a strong candidate for propagating the cellular memory of intrauterine events, causing changes in expression of nearby genes and long term susceptibility to type 2 diabetes.

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Clinical Practice Symposium - Diabetes Session IV Diabetes and Cystic Fibrosis

INV27
Cystic fibrosis – insulin deficiency, early action

C. Verge[a,b]

[a]*Sydney Children's Hospital, Endocrinology, Randwick, Australia;* [b]*University of New South Wales, Kensington, Australia*

Pancreatic destruction in CF causes slow but progressive insulin deficiency. Deficiency of insulin, an anabolic hormone, accelerates the decline of both weight standard deviation score (SDS) and lung function, important predictors of early mortality in CF. Well before the diagnosis of diabetes (as currently defined), elevated glucose levels can be detected by continuous glucose monitoring or the 30-min sampled oral glucose tolerance test (OGTT). These early glucose excursions are associated with detectable glucose in airway fluid, which may promote bacterial growth and progression of lung disease. Current diagnostic criteria for CF-related diabetes (based on 0 and 120-min OGTT blood glucose levels) were originally designed to forecast microvascular disease in type 2 diabetes, rather than CF-specific outcomes such as declining weight or lung function. We analysed OGTTs sampled every 30 min and found that maximum blood glucose (BG) during the test ≥8.2 mmol/l, without diabetes (i.e. 120 min BG < 11.1 and fasting BG < 7), is associated with declining weight SDS and lung function. In the CF-IDEA Trial (Cystic Fibrosis – Insulin Deficiency, Early Action), subjects with these early abnormalities are randomised to once-daily insulin detemir (Levemir) for 12 months, or to observation only. We aim to determine whether starting insulin earlier than current practice will prevent decline in weight SDS and lung function, reduce frequency of hospitalisation, and improve quality of life. Our uncontrolled pilot study using Levemir in this group found that once-daily insulin was accepted by patients, with minimal hypoglycaemia, and resulted in significant weight gain and improved lung function (compared with the 12 months prior to once-daily insulin treatment).

INV28
Cystic fibrosis related diabetes – clinical care

C. Acerini

University of Cambridge, Department of Paediatrics, Cambridge, UK

Up to 9% of patients with Cystic Fibrosis below the age of 10 years have cystic fibrosis related diabetes mellitus (CFRD), with annual age-dependent incidence rates ranging from 4% to 9%. CFRD is progressive and insidious in onset, with the majority of patients having no obvious symptoms at the time of diagnosis. Annual screening using the oral glucose tolerance test (OGTT) from age 10 years is recommended in all CF patients, although CFRD can be diagnosed during episodes of acute illness with fasting plasma glucose levels ≥7.0 mmol/l (or 2-h post-prandial ≥11.1 mmol/l) for more than 48 h.

Achieving good glycaemic control in patients with CFRD is paramount as the degree and duration of hyperglycaemia, and the severity of underlying insulin deficiency, impacts adversely on the rate of decline in pulmonary function and on weight gain; contributing to increased CF related morbidity and risk of mortality. Patents with CFRD may also develop diabetes related microvascular complications for which annual screening is recommended.

ISPAD and CF Foundation guidelines recommend that all patients with CFRD should be reviewed quarterly by a multidisciplinary team with expertise in diabetes and CF. Patients should receive ongoing diabetes self-management education from approved diabetes education programs. Balancing a "standard" CF diet with subcutaneous insulin therapy is the only recommended treatment for CFRD. Patients should perform daily self-monitoring of blood glucose and should attain blood glucose targets as recommended for all people with diabetes.

Few individuals with CF have normal glucose tolerance however. Even when fasting and 2-h OGTT glucose levels are normal, variable, intermittent post-prandial hyperglycemia can often be detected by continuous glucose monitoring. The use of insulin therapy in patients with earlier or "indeterminate" states of glucose intolerance may also benefit weight gain and lung function of CF patients, although this remains uncertain.

INV29
Cystic fibrosis related diabetes (CFRD) and dietary management – clinical practice issues

A.G. Matson

Queensland Health, Allied Health/Adult Cystic Fibrosis Centre, Brisbane, Australia

CF-related diabetes (CFRD) is the main non pulmonary complication of CF with >50% prevalence in adults >40 years. Increased energy expenditure and malabsorption in cystic fibrosis pathophysiology focus nutritional interventions towards the raised energy, fat, protein and salt requirements in this patient population; not "healthy eating". However, Australian trends suggest an individualized approach in management of patients with high BMI may become of greater importance in the next decades.

Insulin insufficiency is the primary pathologic feature of CFRD, and insulin replacement is the only recommended treatment. Insulin therapy stabilizes lung function and improves nutritional status in patients with CFRD. The insulin regimen ideally should fit the patient's lifestyle/diet and meet the needs of their CF management. Dietary intake may be labile or insufficient due to the anorexic effect of infection on appetite alternated with periodic prescription of oral and/or enteral supplements. Insulin cover to match high or fluctuating carbohydrate loads can be challenging; the use of dietary carbohydrate counting and insulin-to-carbohydrate ratios in conjunction with the usual CF diet to guide insulin therapy can help to optimize glycaemic control. Changes in treatment modality, medications, and transplantation also impact nutritional requirements and insulin secretion.

Management of CFRD therefore requires integration of dietary intake data, insulin requirements and assessment of blood glucose response to dietary and insulin therapy. These must be contextualized within the patient's overall CF health status, with consideration also given to the psycho-social interplay of the burden of disease and ability to cope with multiple treatments. Patients with CFRD ideally should be seen quarterly by a specialized multidisciplinary team and receive ongoing diabetes self-management education from diabetes education programs in clinical centres with expertise in diabetes and CF.

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Symposium - Endocrine Session V Pituitary and Pituitary Tumours

INV30
Genetics of pituitary tumors

M.B. Lodish

National Institutes of Health, NICHD, Bethesda, United States

Objectives:

1. Learn the significant advances in the field of genetics of pituitary tumors.
2. Recognize the impact of genetic knowledge on the clinical, diagnostic and therapeutic options for patients with pituitary tumors.

Pituitary gigantism is a rare condition associated with hypersecretion of growth hormone by a pituitary tumor or hyperplasia in childhood, leading to pathological tall stature. In the past few years it has been noted that pituitary gigantism can occur as a feature of a number of monogenic disorders. Approximately 1/3 of acromegaly patients with germline mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene have gigantism, while gigantism can also occur due to mosaisicm for GNAS1 mutations in McCune Albright syndrome or due to PRKAR1A mutations in Carney complex. We recently described a new disorder of X-linked acrogigantism (X-LAG) due to microduplications in chromosome Xq26.3 and up regulation of a G-protein coupled receptor (GPR101). Cushing′s disease is caused by corticotroph adenomas of the pituitary. Although usually sporadic, it may be familial, and is known to occur in the context of MEN-1 and rarely due to mutations of the AIP gene. The finding of a mutation associated with Cushing's disease has clinical implications. Pituitary tumors associated with AIP mutations are larger and present earlier in life. Cushing's disease in MEN-1 often involves multiple pituitary adenomas, which may be larger and aggressive. As a portion of patients continue to have refractory Cushing's disease after surgery, genetic predictors of outcome are useful for determining prognosis. In the last year, a newly discovered gene ubiquitin-specific protease (USP8) has been shown to cause Cushing′s disease via activation of EGF receptor signaling. Somatic mutations in USP8 have been found in 48 (36%) adenomas from patients with Cushing's disease.

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Plenary Session IV Epigenetics

INV31

Mechanisms underlying the developmental origins of metabolic health – insight into intervention strategies

S. Ozanne

University of Cambridge, Cambridge, UK

It is over twenty years since epidemiological studies revealed that there was an association between patterns of early growth and long-term risk of traditionally adult on-set diseases such as type 2 diabetes. This led to the concept of the developmental origins of health and disease – the idea that the environment to which we were exposed during critical periods of development, such as the in utero period, had a permanent impact on our long-term health. One important early environmental factor known to have such programming effects is nutrition. Initial focus was directed towards the detrimental effects of low birth weight and early under-nutrition. However in light of the growing epidemic of obesity, more and more focus is now being directed towards the detrimental effects of early over-nutrition. Fetal under-nutrition and fetal over-nutrition appear to have the same phenotypic consequences in terms of metabolic disease risk. However it is yet to be established if the effects are mediated through the same mechanistic pathways. Animal models have been invaluable in identifying the mechanisms underlying developmental programming. Many rodent models, which enable study across the life course, have been established to mimic the human situation. From such studies three key programming mechanisms have emerged: (i) permanent structural changes – the idea that if during a critical period of development an organ is exposed to a suboptimal level of a key hormone or nutrient required for its development this will permanent impact on organ structure and consequently function, (ii) accelerated cellular ageing of key metabolic and reproductive tissues as a consequence of increased oxidative stress and (iii) epigenetic programming of gene expression through changes in DNA methylation and/or histone modifications. Further understanding these mechanisms may give us the potential to ultimately develop markers of disease risk and help in the design of rational intervention strategies.

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Symposium - Diabetes Session VII Are We What We Eat? Nutrition and Diabetes

INV32
The role of the microbiome in the pathogenesis of type 1 diabetes – what do we know?

A. Heintz-Buschart[a], C. de Beaufort[a,b] & P. Wilmes[a]

[a]*University of Luxembourg, Luxembourg Centre for Systems Biomedicine, Esch-sur-Alzette, Luxembourg;* [b]*Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg*

The human body hosts multifarious ecosystems of microorganisms, collectively termed the human microbiome. The gastrointestinal tract (GIT) harbours the greatest number of microbial cells and richness of different taxa. The GIT microbiome is recognized as essential to nutrition and digestion, and in shaping the immune system. More recently, changes in the GIT microbiome have been linked to the development and progression of a number of idiopathic human diseases.

Several studies have looked for and identified differences in the composition of the microbiome of children with and without T1DM, sometimes observing a clear enrichment of certain bacteria or viruses in affected individuals. However, studies at different geographical locations, with different cohort sizes and different analytical methods have not been able to identify a common putative causative agent. Even the more commonly observed decrease in microbial diversity, which is often associated with a less beneficial microbiome, was not reproduced in all studies. For T1DM, no conclusive mechanistic role for the GIT microbiome has yet been put forward, but animal studies point to its essential immune-regulatory role. However, all studies that have looked at functions of the microbiome in addition to enumeration have found subtle differences in the microbiomes' functional capacities. These differences may be associated with varying taxa in different individuals, depending on genetics and exposure, which will also influence the impact of these differences on human physiology. Here, we will summarize recent observations from studies of the GIT microbiome before, during and after the onset of T1DM and discuss perspectives. Future studies will have to take into account the individual genetic and environmental background of the studied individuals, and focus on functional analyses of the microbiomes to elucidate detrimental interactions with the human host to ultimately inform clinical practice.

INV33
AGEs in our diet: where do they go and why?

J.M. Forbes[a,b,c]

[a]*Mater Research Institute-The University of Queensland, Glycation and Diabetes, Brisbane, Australia;* [b]*University of Queensland, School of Medicine, Brisbane, Australia;* [c]*Translational Research Institute, Brisbane, Australia*

Advanced glycation end products (AGEs) are formed in the body when lysine and arginine residues in proteins and peptides become irreversibly modified by reactive sugars or carbonyls. AGEs can also be absorbed from dietary sources, in particular from westernised diets where they are formed a result of modern food processing, storage and choice of cooking method. AGEs are arguably best studied in diabetes complications where increased burden of AGEs in the body, measured at sites such as the skin and within the circulation, can predict the later onset of diabetic complications. Recently, however, there has been a paradigm shift which suggests that AGEs, including those from dietary sources, may be direct modulators of insulin secretion and peripheral insulin sensitivity and as such, may play a crucial role in the development of both major forms of diabetes *per se*. There is also evidence for kidney damage as a direct result of AGEs, independent of glycaemic control, which may also influence mortality. The major effects of are most likely mediated via ligation with receptors such as the receptor for advanced glycation end products, RAGE but also with another relatively novel AGE receptor, AGE-R1. The signalling of AGEs via receptors is known to influence inflammatory and immune cascades and metabolic pathways involved cell growth and energetics.

INV34
What have nutritional trials taught us in diabetes in children and adolescents?

P. Clifton

University of South Australia, Adelaide, Australia

In type 2 diabetes in adolescence there are no published nutrition or lifestyle monotherapy interventions. In the TODAY study there was no additional benefit of lifestyle when added to metformin. The TODAY study is very valuable in highlighting the high incidence of hypertension, microalbuminuria and retinopathy after 3 years. This strongly suggests interventions need to occur early in obese and overweight children with insulin resistance, prediabetes and metabolic syndrome and there are a modest number of trials (16) which show benefit in terms of weight loss and insulin sensitivity with no differences with macronutrient composition. Omega 3 fats reduce carotid IMT in high risk children. More trials on vascular function and structure are required in both type 1 and type 2 diabetes.

In type 1 diabetes most focus has been on dietary strategies to manage intensified treatment without an increase in serious hypoglycemia. Less attention has been paid to reducing the enhanced vascular risk in type 1 diabetes although the EURODiab study in adults predominantly has shown the effects of saturated fat, fibre and exercise on influencing CVD events and mortality and fish intake on microalbuminuria. Exercise in youth with type 1 DM is very beneficial for dyslipidemia and blood pressure as is folic acid for endothelial function. L-arginine does not appear to be helpful. In children with antibody positive type 1 diabetes baseline omega 3 levels and leucine levels predicted preservation of C peptide levels at 24 months in the group with a fasting C peptide of >0.23 ng/ml.

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Symposium - Diabetes Session V ADA/ISPAD Symposium: The Rights of the Individual with Diabetes

INV35

Diabetes and disability – how well do we do?

M. McDowell[a,b]

[a]*Child Development Network, Brisbane, Australia;* [b]*University of Queensland, Paediatrics, Brisbane, Australia*

Diabetes and disability share the complexity of longitudinal care. Alongside presenting clinical need runs a parallel thread of consideration towards the long term. As health professionals, we want each child to be in the best condition as they transition into adult life. This long-term goal means more than just minimisation of disorder-related harm. It also includes optimisation of how each individual adapts to their life situation.

In both fields there is a large and growing body of research knowledge informing evidence based practice (EBP). The limitation of EBP, however, is that intervention research requires controlled situations, and tends to consider relatively short time frames. It does not easily address the question of how best to set up for, and achieve over time, optimal long-term outcomes.

In this talk I will introduce complex systems (CS) theory as a model for considering the complexity that arises as multiple factors interact over time. The models of CS do not enjoy the direct mathematical relationships between dependent and independent variables that are assumed in most of EBP research. They can, however, lead to interventions and predictions that are testable experimentally and incorporate the complexity of individual factors for each child.

I will apply CS principles to the care of a pre-pubertal child presenting with diabetes, who also has developmental problems with learning, working memory and impulse control. In addition to the expected turbulence of emerging teenage self-determination, this child is is likely to be at greater risk of poor diabetic control during their adolescence. Issues such as self-image, planning, impulse control, peer relationships, school experience and more, all contribute to the final common pathway of diabetic stability.

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Symposium - Diabetes Session VI VIDIS Symposium

INV36
DiViD study. What can we learn from pancreatic biopsies?

L. Krogvold[a,b,c]

[a]Oslo University Hospital, Oslo, Norway; [b]University of Oslo, Oslo, Norway; [c]Oslo Diabetes Research Centre, Oslo, Norway

Despite intensive research efforts over the past century, the precise causes of type 1 diabetes are still unknown. This is partly due to lack of studies of fresh pancreatic tissue from patients at diagnosis. In the Diabetes Virus Detection Study (DiViD) fresh pancreatic tissue was collected with laparoscopic tail resection from six live adult individuals (aged 24–35 years) three to nine weeks after the diagnosis of type 1 diabetes. The collected material was of optimal quality and processed in various ways. This allowed many different analyses and investigations in close cooperation with different research groups all over the world. This lecture will, among other aspects, focus on:

- Function of isolated live islets and possible restoration after some days in a non-diabetogenic environment.
- The insulitis, insulin containing islets and characterization of infiltrating T cells in pancreas at onset of T1D.
- The detection of a low-grade enteroviral infection by different methods in the islets of Langerhans.
- The gene expression in laser captured islets, compared to the gene expression in non-diabetic organ donors.

In addition, the status of ongoing and planned studies will be reviewed.

INV37
Enteroviruses and the immunopathology of type 1 diabetes

N.G. Morgan

University of Exeter Medical School, Institute of Biomedical & Clinical Science, Exeter, UK

Type 1 diabetes is increasing in incidence in many populations and this cannot be attributed to genetic factors. Rather, the data imply that specific environmental factors must be critical determinants of disease. Among such factors, an increasing weight of epidemiological evidence, derived from multiple population studies, has implicated infection with enteroviruses in the disease process. Despite this, absolute causality remains unproven and the molecular events that might lead from enteroviral infection to diabetes development have not been established. To address this, we have undertaken a detailed analysis of the molecular pathology of type 1 diabetes in human pancreas samples collected from patients who died soon after developing the illness. This has confirmed that enteroviral infection occurs much more frequently in the islet beta-cells of patients with type 1 diabetes than in relevant controls. It has also revealed some of the cellular events associated with enteroviral infection which may precipitate islet autoimmunity.

We propose that type 1 diabetes occurs when an atypical "persistent" enteroviral infection develops in islet beta cells. This involves molecular changes to the structure of the viral genome and is accompanied by the development of a robust anti-viral response by the cells, leading to altered antigen presentation. The response involves activation of innate pattern recognition receptors, the elaboration of interferons, increased islet cell expression of MHC class-I antigens and attendant changes in antigen presentation.

Considering this evidence as a whole, a model will be evaluated in which the "strength" of the β-cell response to the establishment of a persistent enteroviral infection may determine the final disease outcome. As such, these new insights suggest mechanisms by which intervention might be possible to reduce or halt the rate of beta-cell loss in patients at risk of developing type 1 diabetes.

INV38
Gene-environment interactions in type 1 diabetes – what can we learn from other diseases?

A.-L. Ponsonby

Murdoch Childrens Research Institute, Royal Children's Hospital, University of Melbourne, Population Health, Melbourne, Australia

It is becoming increasingly recognized that many determinants of autoimmune disease, both genetic and environmental are shared across autoimmune diseases. The involvement of gene variants in autoimmune disease is well established, and evidence for significant involvement of the environment in various disease forms is growing. These factors may act independently, or they may interact, with the effect of one factor influenced by the presence of another. Identifying combinations of genetic and environmental factors that interact in autoimmune disease has the capacity to more fully explain disease risk profile, and to uncover underlying molecular mechanisms contributing to disease pathogenesis. Environmental effects on immune responses could be mediated by changes in epigenetic regulation. Major mechanisms of epigenetic gene regulation include DNA methylation and histone modification. In turn, such knowledge is likely to contribute significantly to the development of personalised medicine, and targeted preventative approaches. Here, I consider the current evidence for gene-environment interaction in autoimmune disease and particularly how this could inform our understanding of the biological processes underpinning type 1 diabetes mellitus.

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Clinical Practice Symposium - Diabetes V APPES/ISPAD Symposium: Using Guidelines to Improve Clinical Care in Developing and Developed Countries

INV39
Standard setting in diabetes – NICE work if you can get it

J. Wales[a] & NICE Diabetes in Children and Young People Clinical Guideline Group

[a]*Lady Cilento Children's Hospital, Endocrinology & Diabetes, South Brisbane, Australia*

Good audit and research are the foundations for standard setting in diabetes. International audit has shown wide variation in diabetes control between centers. National audits have shown year-on-year improvement can be achieved by the application of rigorous standards based on clinical evidence.

The National Institute for Health & Care Excellence (NICE) in England and Wales is recognized as a body that produces high quality evidence-based recommendations and health economic analysis for care, and in 2015 produced an update of previous 2004 guidance on standards of care for diabetes in children and young people.

For the first time the guidance included childhood type 2 diabetes and the treatment of diabetic ketoacidosis. (Monogenic diabetes and CF-related diabetes were not included in the scope of the review which was co-published with guidance on adult type 1 & 2 diabetes and diabetes in pregnancy).

The guideline has recommended an ambitious clinic aim for near normoglycaemia & HbA1c with individual target setting and an emphasis on the support and treatments required to achieve these goals.

The process and personnel used to construct the guidance will be discussed, as well as the "highlights" of the recommendations and areas where no evidence exists and more research is required.

Adoption of the standards will inform the audit process in England & Wales (and NHS funding for diabetes services in England) and hopefully further drive improvements in care.

INV40
Challenges of using and meeting clinical guidelines in India

V.V. Khadilkar

Jehangir Hospital, Pune, Pediatric Endocrinology, Pune, India

Challenges can broadly be classified into economic, socio-cultural, medical, school and infrastructure related.

Economic: Less than 15% of Indian states have free insulin availablility. Insurance companies do not covers outpatient diabetes management. All the funding is provided by families from their pockets.

Socio-cultural: Dietary modifications required to live with diabetes are unacceptable to families. Assessment of carbohydrate content of Indian diet remains a challenge due to variability in cooking practices. Acceptance of 4 injections a day is poor. Lack of education in parents leads to inability to note down, understand and act on the HMBG values. Percentage of patients on basal bolus therapy is 30% in lower and 70% in upper socioeconomic classes. Use of alternative medicines leads to inconsistent management. Concealing the diagnosis of diabetes from friends and school makes it hard deal with emergencies.

Medical facilities: Multidisciplinary clinics and 24 h help lines are available at only handful hospitals and almost no psychological support is available for children and families as outreach service. We found depression in 70% parents in our study. Recognizing DKA remains a challenge due to unavailability of glucometers and unawareness of diabetes amongst medical practitioners in many remote places. There is scarcity of intensive care units and trained doctors. Tests that have to be performed as per the protocol are beyond affordability of the majority.

Infrastructure and school: Lack of electricity, refrigerators, and cold chain maintenance remains a problem. In cities children have an average travel time of 1–2 h to reach schools and long school hours (6–8 h/day) makes it hard to plan meals and administer insulin. Around 4% schools in cities have a school nurse and refrigerators are not available in 20–30% schools in cities and no school in villages have fridges.

Thus there is a need to modify guidelines to meet these practical challenges.

INV41
Adaptation and implementation of guidelines in developing countries

G.D. Ogle[a,b]

[a]*International Diabetes Federation, Life for a Child Program, North Epping, Australia;* [b]*Diabetes NSW, Glebe, Australia*

Clinical guidelines are essential for standardised, competent care across a health system. Some less-resourced countries have national guidelines for management of type 2 in adults, but very few have guidelines for management of type 1 in children and adolescents. The most widely used international guideline is the Clinical Practice Consensus Guideline of the International Society for Pediatric and Adolescent Diabetes (ISPAD). However, with the advent of evidence-based medicine, and ever-more complex treatment options and considerations, these guidelines have by necessity become long and complex. For example, if a doctor inexperienced in type 1 suddenly has to care for a child who without good care would soon die from diabetic ketoacidosis (DKA), what do they do? – they need simple, clear instructions to safely correct the DKA, initiate regular insulin therapy, educate the family, and monitor progress. All this needs to be within the context of available resources.

LFAC and ISPAD therefore developed the "Pocketbook for Management of Diabetes in Childhood and Adolescents in Under-resourced Countries". Content was sourced from the ISPAD guidelines and other materials. The final version was released at the IDF Congress in Melbourne in 2013. It is A5 size, 54 pages, and covers definition and diagnosis, management of DKA, insulin therapy, hypoglycemia, sick day management, blood glucose monitoring, nutrition, physical activity, complications, psychological care, adolescent issues, diabetes in schools, and pregnancy.

It has been distributed to the 48 nations participating in LFAC and is available on IDF and ISPAD websites. Translations are proceeding. Reception has been very positive. A further need has been identified – for simple wall charts that contain the key management protocols in the guidelines – LFAC is preparing these. National guidelines, fully tailored to local resources, can also now be more easily developed using the Pocketbook as a base.

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Symposium - Endocrine Session VI Turner Syndrome

INV42
Optimizing hormone replacement therapy in girls with Turner syndrome (TS)

C.A. Quigley

Indiana University, Pediatric Endocrinology, Indianapolis, USA

Ovarian dysgenesis is a cardinal feature of TS, and while the primary clinical manifestation of ovarian failure is absent or incomplete secondary sexual development, the estrogen deficiency in TS begins at birth and likely has significant consequences for physical and psychological well-being from infancy onward. Although estrogen replacement to induce puberty has been standard of care for TS since the 1960s, treatment was often delayed until the mid-teen years because of long-held concerns regarding the role of estrogen in advancing skeletal maturation and truncating linear growth. Furthermore, while data from the mid-1990s demonstrated that healthy prepubertal ovaries secrete measurable amounts of estradiol [1], the concept of childhood estrogen replacement at very low dosages with the intent of replicating the prepubertal hormonal milieu rather than inducing feminization, has been largely unexplored. Limited data from studies of childhood low-dose estrogen replacement in TS demonstrate unimpaired height gain and more physiologic pubertal timing [2–4].

In addition to timing of estrogen initiation, other key unresolved questions concern route of administration, tempo of escalation and timing for addition of progestins. While opinion is mounting in favor of transdermal estrogen [5,6], data from prospective, randomized, controlled trials are lagging [7,8]. Additional controlled data are needed, followed by prospective observational studies through adulthood to assess long-term outcomes potentially affected by estrogen deficiency and replacement, such as autoimmune, bone, cardiovascular, cognitive, metabolic and psychosexual wellbeing.

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INV43
Improving cardiac surveillance and cardio-metabolic risk in Turner syndrome

C. Gravholt

Aarhus University Hospital, Department of Endocrinology, Aarhus C, Denmark

Treatment with growth hormone (GH) during childhood and adolescence allows a considerable gain in adult height. Puberty has to be induced in most cases, and female sex hormone replacement therapy should continue during adult years. These issues are normally dealt with by the paediatrician, but once a TS female enters adulthood it is less clear who should be the primary care giver. Morbidity and mortality is increased, especially due to the risk of dissection of the aorta and other cardiovascular diseases, as well as the risk of type 2 diabetes, hypertension, osteoporosis, thyroid disease and other diseases.

The proper dose of hormone replacement therapy (HRT) with female sex steroids has not been established, and, likewise, benefits and/or drawbacks from HRT have not been thoroughly evaluated. In most countries it seems that the transition period from paediatric to adult care is especially vulnerable and the proper framework for transition has not been established. Likewise, no framework is in place for continuous follow-up during adult years in many countries. Today, most treatment recommendations are based on expert opinion and are unfortunately not evidence based, although more areas, such as GH treatment for increasing height, are well founded.

During the transition period many young females opt out of longitudinal follow-up, probably because they feel well and cannot clearly see the need for continued medical surveillance. However, osteoporosis, diabetes, both type 1 and 2, hypothyroidism, obesity and a host of other endocrinological diseases and conditions are seen more frequently in Turner syndrome in the long term. Prevention, intervention and proper treatment is only just being recognized. Hypertension is frequent and can be a forerunner of cardiovascular disease.

In summary, Turner syndrome is a condition associated with a number of diseases and conditions which need the attention of a multi-disciplinary team during adulthood.

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Plenary Session V JDRF Symposium: Cutting Edge Technology

INV44
Using technology to reduce hypoglycaemia

T. Jones

University of Western Australia, Perth, Australia

Hypoglycaemia and fear of hypoglycaemia remain significant problems in the management of Type 1 Diabetes. Although hypoglycaemia rates have fallen in the last decade, patients are still exposed to hypoglycaemia risk and this in turn affects quality of life and places a barrier to attempts to improve glycaemic control. In addition, impaired awareness of hypoglycaemia may occur in youth with Type 1 diabetes and places patients at even increased risk. Recent developments including insulin dosing aps, real time CGM, algorithms linked to pump insulin delivery that suspend insulin on hypoglycaemia or predicted hypoglycaemia and closed loop insulin delivery have all offered potential to reduce hypoglycaemia and hypoglycaemia fear. Because of the rate of change and introduction of these new developments it will be important to establish their place in diabetes management.

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