

Invited Speakers

INV01

The state of the world's children with diabetes

D. Daneman

Hospital for Sick Children/University of Toronto, Pediatrics, Toronto, Canada

The Ecological Perspectives Model proposes that health care outcomes depend on factors operative in five domains: societal, community, institutional, interpersonal and intrapersonal. This model applies effectively to outcomes in children with diabetes: the macroenvironments of these children (defined by factors in the societal, community and institutional domains) vary enormously both in terms of diabetes incidence/prevalence as well as resources available for their care and diabetes-related morbidity and mortality. Similarly, the microenvironment (inter- and intrapersonal domains) will dictate the quality of diabetes-specific outcomes, including metabolic control, acute and long-term diabetes-related complications, quality of life, and self-esteem. This presentation will focus on the evidence available as well as the reality of outcomes achieved. Specific barriers to achieving and maintaining excellent diabetes 'health' depends not only on the availability of appropriate resources, but also on the personal and family reliance to use these resources to the best of their abilities.

INV02

Goals of diabetes care

T. Danne

Kinderkrankenhaus auf der Bult, Diabetes Center for Children and Adolescents, Hannover, Germany

The goal of pediatric diabetes care is to avoid the long term micro- and macrovascular complications of diabetes through near-normoglycemic metabolic control. Equally age-appropriate somatic and psychosocial development and good quality of life has to be ensured in the context of the resources of families or caregivers. Target glycemic levels have to be adapted in view of the local availability of insulin preparations, devices and equipment for self-blood glucose monitoring. In setting individual goals the psychological and social impacts of weight gain and puberty as well as avoiding acute complications such as hypoglycaemia and other side effects of treatment have to be considered. With evidence for a 'metabolic memory' accumulating, glycemic control is important to prevent or delay long-term complications from the very beginning also in the paediatric age group. The HbA1c currently is the best surrogate parameter for control. Many teams have adopted a target HbA1c-value of below 7.5% for all pediatric age groups. Novel technologies for continuous glucose monitoring have the advantage of providing information about the direction, magnitude, duration, and frequency of glucose excursions for up to 7 days with a single sensor. As glycemic variability is implicated in the pathogenesis of complications, reducing glycemic variability with the help of these devices may become a future goal also in pediatric diabetes. Presently even in industrialized countries with excellent health care availability significant differences in the attainment of these goals have become evident. Therefore collection of data on glycemic control from each diabetes center for comparison with stated local, national and international standards should be implemented so that the performance and standards of the interdisciplinary diabetes care teams may be improved. Data from the Hvidovre Group indicate that clear and consistent setting of glycemic targets by diabetes teams is strongly associated with HbA1c outcome in adolescents. Target setting appears to play a significant role in explaining the differences in metabolic outcomes between centers. To improve outcomes through sharing of best practices, ISPAD collaborates with IDF

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Europe, FEND, PCDE, and national diabetes organisations in a new project called SWEET, which is co-funded by the European Public Health Agency (PHEA). It aims at better control in pediatric and adolescent diabetes in the EU by creating Centres of Reference.

INV03

Poverty as a confounding factor in diabetes care

A. Virmani

New Delhi, India

In 2001, 1.1 billion people worldwide were living in "extreme" poverty (consumption < \$1 a day). Of them, a third were in India, in spite of recent high economic growth, which reduced the extremely poor from 31 to 21.8% [2004–05]. The poor are economically, socially and educationally deprived: most are unorganised workers, with no social protection, job security, regularity of wages, adequate earning capacity, or ability to upgrade skills. They have weak social networks, poor access to information, and discriminatory social milieu. They can be pushed deeper into poverty by even minor illnesses, leave alone lifelong illnesses. However, NGOs and Governments are making a difference. Developed countries have a high ratio of public health spending to private spending. In developing countries, either private spending dominates or both private and public spending are low. India has the lowest ratio of public: private health expenditure (< 1:4.5); public health spending is < 1% of GDP; and private spending is out-of-pocket. This is inherently regressive, putting a disproportionate burden on the poor. Public health systems are often not geared for chronic disorders; low cost options may not be used by corporate/governments. Childhood diabetes particularly faces political and even medical apathy. Poorly nourished women have more small for date (SFD) babies, who at higher risk of metabolic syndrome later. At present, many of them remain thin, physically active adults, but obesity and type 2 diabetes is increasing among the poor. Poor fetal/infant nutrition impacts brain development, making management more difficult. Poverty hits all aspects of diabetes management. Diagnosis may be delayed/missed due to lack of awareness/glucose test strips, with children in DKA dying undiagnosed. Insulin is expensive; other issues are:

- Cold chains: may fail because of erratic electricity, affecting the quality of insulin.
 - Storage after purchase: is difficult without refrigerators. We showed that insulin can survive 44C for 2-4 weeks in water in mud pots, but this awareness is not widespread.
 - Availability: is limited in remote areas.
 - Affordability: no income for a few days may stop a child's insulin, with DKA/death.
 - Communication: product inserts are often not available in local languages.
 - Insulin syringe reuse: information is poorly disseminated.
 - Safety: devices for safe disposal of needles are often unavailable. Weak liability regulations allow syringe/insulin companies to ignore safety aspects.
- Inadequate or no monitoring means even fair glycemic control is difficult:
- BG meters are costly, difficult to repair/replace, need special batteries.
 - Strips are costly, and reducing costs is difficult. Color matching strips (could be halved, eliminated need/cost of meter/batteries) have been phased out.
 - Illiteracy makes increasing awareness and even reading/recording BG difficult.
 - A1c/other tests for chronic complications are costly, often unavailable.

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All complications are thus commoner; mortality is higher; employability, income, and quality of life are worsened; cost of care further increased: a vicious cycle. Some problems ease management, e.g. being conditioned to obey and not question can help compliance; physical activity helps; families do provide support.

Diet worsens matters:

- Agricultural policies focusing on rice/wheat production; polished rice means low fiber with high carb
- Hot climates/little refrigeration means intake of diabetogenic fried foods
- Fiber is underutilized (lack of awareness) and hard to afford in cities
- Aspirations of upward mobility, mass production making junk foods cheaper, and cynical marketing strategies encouraging their intake, worsens nutrition.
- Pulses and milk are expensive: so protein & calcium deficiencies rampant.

Social issues:

- a. Discrimination: in education, employment, and marriage because of low awareness and chronic ill health.
- b. Social security: unavailable to > 90% population.
- c. Quacks: are sought since modern medicine is costly.
- d. Gender: discrimination worsens all handicaps for females.

Urbanization packs the poor into unhygienic slums, but increases earning (especially women), reduces social and health taboos, and increases access to health care. As colonies become free, better political/financial environment has improved access to facilities. These problems must be understood and quantified to allow coherent and comprehensive policy making. Thus science is married to economics and politics, promoting health and well being, increasing economic growth and providing equity.

INV04

Challenges to diabetes care: Costa Rica

E. Richmond

National Childrens Hospital, Pediatric Endocrinology, San Jose, Costa Rica

Costa Rica is a small country with an interesting characteristic: it has a third world economy and has first world health indicators. This condition is challenging diabetes care in children. Costa Rica, a tropical country, located in Central America, has an area of 51,100 squared meters and a population of 4.5 million. The literacy rate is 95% defined as 10 years or more of education, unemployment is 6%. Democracy has been stable for many decades and there is no army since 1949. Main activities are tourism, agriculture and high technology. In terms of economy, is considered a third world country, with a per capita income of approximately \$13,500, compared to first world countries as USA with a per capita income of approximately \$ 50,000. In terms of health care, Costa Rica has similar health indicators as those in first world countries. Infant mortality in Costa Rica is 9.7 (deaths in the first year of life per 1,000 newborns), in USA is 6.5. Life expectancy in Costa Rica is 79 years and in USA is 78. The public national health system covers 90% of the population, approximately 10% of the population uses private practice resources. There is only one pediatric hospital in the country, there are seven general hospitals with pediatric and neonatal units spread through the country and hundreds of clinics and small hospitals. All children with new onset diabetes are admitted at the National Children's Hospital and seen by the pediatric team, including pediatric endocrinologist, nutritionist, nurse, social worker and psychologist. Two studies by our team

describe diabetes care in children younger than 15 years of age. The first study was done between 1999 and 2001, we reviewed the clinical charts of 111 children with type 1 diabetes. The average age at diagnosis was 8.89 ± 3 years. The average HbA1C level was $7.75\% \pm 2.07$ (excluding the first 6 months after diagnosis). 96% of the patients were on at least three insulin shots per day and all were performing multiple blood glucose monitoring at home. In the second study (2002–2006), we retrospectively analyzed all new onset diabetic patients in our institution. A total of 239 new diabetics presented during the 5 years of the study. 204 (85%) patients were classified as type 1 and 35 patients (15%) classified as type 2 or other types of diabetes. The incidence of type 1 diabetes was 3.54/100,000/year, which is considered a low incidence based on the World Health Organization parameters. Within the type 1 diabetes group, in the second study, 50% of the new onset diabetics presented without ketoacidosis (bicarbonate). In terms of diabetes care in children, Costa Rica is facing many challenges, including: (i) economic strategies to continue intensive diabetes control in all patients, (ii) to improve diabetes education, (iii) to increase the number of diabetes nurse practitioners, (iv) to increase the number of patients using insulin analogues, (v) to start using insulin pumps, and (vi) to prepare protocols for management of increasing numbers of type 2 diabetes in children. ³ 15), 17% presented with mild ketoacidosis (bicarbonate: 10–14), 22% with moderate ketoacidosis (bicarbonate: 5–9), and 11% with severe ketoacidosis (bicarbonate < 5), including one patient who died secondary to brain edema. After the acute phase, all patients were discharged on intensive insulin therapy, only ten patients were prescribed glargine insulin at bedtime and lispro insulin before meals, the rest of the patients were started on regular insulin before meals and NPH insulin at bedtime.

INV05

Early origins of adult disease: the role of infant nutrition

D. Wittenberg

University of Pretoria, Paediatrics and Child Health, Pretoria, South Africa

Accumulating evidence from many parts of the world has linked the developing fetus' and young infant's nutritional environment to epigenetic programming that may predispose the organism to specific identifiable health risks in later life. Initially, predominant attention was given to insufficiency or excess of nutrition during gestation and early infancy. Increasingly, the actual composition and balance of nutrients is also linked to nutritional programming during critical periods of adaptation. Developmental programming aims to prepare the organism for optimal survival in the predicted future environment. The thrifty phenotype hypothesis links a mismatch between programming and later nutritional environment to the development of obesity, the metabolic syndrome and cardiovascular risk. Epigenetics refers to changes in gene function that occur without a change in gene sequence. DNA methylation contributes to conformational change in chromatin during periods of enhanced epigenetic lability that can repress transcription activation and 'silence' associated genes. A temporal association between the decline of breastfeeding and the rise of the obesity epidemic prompts questions regarding the role of high protein infant feeding in nutritional programming. In this paper, we review the evidence linking the type and quantity of dietary protein exposure in early infancy to metabolic and endocrine responses and growth patterns that are associated with later risk of chronic disease.

INV06

The fetal origins of insulin resistance

C. Levy-Marchal

UNITE 690 INSERM, Hôpital Robert Debré, Paris, France

Over the last 15 years a number of long-term health risks associated with reduced fetal growth and/or low birth weight have been identified, including cardiovascular diseases, hypertension, dyslipidemia, or type-2 diabetes. A common feature of these conditions is insulin resistance, which is thought to play a pathogenic role. Insulin resistance develops early in life, as early as the first year of life. It is modest in magnitude but it contributes to the development of diabetes and the metabolic syndrome. In a population-based cohort of young adults the prevalence of the metabolic syndrome was 2.3% in subjects born SGA in comparison to 0.4% in AGA. The phenotype of lower birth weight associated with higher body mass index in childhood and adulthood appears to predict the highest risks of insulin resistance and cardiovascular events, pointing to the crucial role of catch-up growth in relation to fetal growth restriction. Despite abundant data in the literature, it is still difficult to trace the pathway by which fetal events, environmental or not, may lead to the increased morbidity later in life. To explain this association, several hypotheses have been proposed pointing to the role of either a detrimental fetal environment or a genetic susceptibility or an interaction between the two and of the particular dynamic changes in adiposity that occurs during catch-up growth. It has been suggested that thinness at birth may affect muscle structure and function and impair carbohydrate metabolism, as shown by reduced rates of glycolysis in muscle of adult subjects born with low ponderal index. However, how it is linked to insulin resistance is unclear. Postnatal catch-up is a compensatory phenomenon to abnormal thinness or smallness at birth in order to bring each subject to his/her spontaneous "genetic" centile. However, catch-up growth likely promotes an excess of adiposity in relation to muscle mass. Furthermore, in studies focusing on body composition and fat distribution, low birth weight has been associated with a more central pattern of fat distribution. Adipose tissue in SGA individuals follows a shows a very specific pattern of growth and shows changes in function such as hypersensitivity to catecholamines, reduced secretion of adipokines. There have been so far very few intervention studies to interfere with the natural course of insulin resistance in SGA. It has been reported that both quantitative and qualitative changes in nutritional intake of the mother can induce fetal metabolic programming and that there are several time-windows during which the process can be initiated.

INV07

Management of obesity

C. Maffeis

Section of Pediatrics, Department of Mother and Child, Biology-Genetics, Regional Centre for Juvenile Diabetes, University of Verona, Italy

Treatment of obesity is much more effective in children than in adults. Family is the object of treatment, especially in pre-adolescents. Adolescents need to be approached individually and, separately, the parents. The therapy of obesity should aim to the modify factors promoting fat gain and fat maintenance. Primary obesity is a complex disease, due to the interaction of multiple genetic and environmental factors. More than 430 genes have been variably associated with obesity. However, the phenotype expression of the genetic factors predisposing to obesity needs environmental exposition. The triggering effect of environment

leads to behaviour changes of the predisposed individual causing a prolonged positive energy balance. Therefore, fat mass increase is the epiphenomenon of all the factors, both genetic and environmental, that promote an increased energy (and nutrient) intake in respect to energy (and nutrient) requirement. On the basis of the above mentioned considerations, the first target of the treatment of childhood obesity is to make changes in the behaviour to promote a prolonged negative energy (fat) balance, leading to fat mass reduction. Nutrition and physical activity habits have to be persistently modified in obese children. Intervention on nutrition should encourage changes in food preferences, reducing energy intake and diet density, by increasing the carbohydrate/lipid ratio and fibre intake, and promoting healthy eating patterns. Glucose oxidative and non-oxidative disposal in the skeletal muscle affects insulin sensitivity. Therefore, skeletal muscle activity plays a key role in the metabolic regulation of the organism. Substituting part of the time spent in sedentary behaviour with light to moderate intensity activities is the first step. Low intensity and prolonged aerobic exercise is preferable to high intensity exercise, since the lower the exercise intensity, the higher the fat oxidation rate. Efficacy of reducing sedentary behaviour has been demonstrated. Obesity is associated with a reduction of spontaneous physical activity and external work capacity, in spite of the peak energy expenditure (peak VO₂) per unit fat-free mass is similar to that of non-obese children. Therefore, exercise programmes should be designed on the basis of the peak VO₂ of the child to maximize the compliance and the efficacy of the exercise itself. The role of the time spent in moderate to high intensity exercise in preventing obesity has been demonstrated whereas its independent role in treating childhood obesity is less clear at the moment.

Drugs: FDA approved the use of Orlistat, a lipase inhibitor, for treating obese adolescents. In combination with diet, exercise, and behavioral modification, orlistat statistically significantly improved weight management in a group of 357 obese adolescents compared with placebo. The use of orlistat for 1 year did not raise major safety issues although gastrointestinal adverse events were more common in the orlistat group. Sibutramine, a serotonin and norepinephrine re-uptake inhibitor, was found to be useful together with behavioural therapy in the treatment of obese adolescents but FDA has not approved yet the use of this drug for children or adolescents.

Surgery: An international consensus on the indications of surgery for treating morbid obesity in adolescents resistant to conventional treatment still needs to be found.

INV08

Type 2 diabetes in youth

W. W. R. Lee

KK Hospital and Camden Medical Centre, Singapore

Type 2 diabetes in children and adolescents was actually described in 1973 but widespread recognition of this problem has only happened in the last 10–15 years. The typical patient is obese, often pubertal, and has a family history of Type 2 diabetes or gestational diabetes. There may be no symptoms at all, or typical symptoms of weight loss, polyphagia and polyuria may be present. Sometimes the patients can present in diabetic ketoacidosis. A low or absent insulin level at diagnosis does not necessarily exclude the diagnosis. In most cases, the GAD and Islet cell antibody tests will be negative. Classification and recognition of this entity at presentation may be difficult and the diagnosis of Type 1 vs Type 2 diabetes may have to be revised time. However, it is known that while reversal of symptoms of diabetes can occur, paediatric and adolescent diabetes can have a 15% decline in pancreatic insulin

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production per annum. Case finding is complicated by the finding of normal fasting but abnormal 2 hour post OGTT readings. Mass urine screening, directed screening of high risk groups and have been tried. Diabetes complications can present early and are not milder than those seen in Type 1 diabetes mellitus. Components of the metabolic syndrome may be present at diagnosis or soon after. Treatment should be directed at 5 aspects :

- replacement of insulin levels using oral agents or insulin injections,
- improvement of insulin resistance using oral agents such as Metformin,
- prevention of complications through good glycemic control and a systematic complications screening programme
- treatment of co-morbidities such as hyperlipidemia, hypertension, microalbuminuria, eye complications, and fatty liver
- addressing the root causes – such as teen obesity, lack of exercise, obstructive sleep apnoea, etc.

The drugs of choice are metformin and insulin. Metformin because it is a cheap, proven, relatively safe oral medication. Insulin because it addresses the relative insulinopenia immediately and allows recovery of islet cell function over time. It is also important to treat comorbidities such as hypertension for age, obstructive sleep apnoea, fatty liver, hyperlipidemia and obesity. roviding equity.

INV09

Novel cellular therapies for the prevention and amelioration of type 1 diabetes

D. Schatz

University of Florida, Pediatrics, Gainesville, FL, USA

Despite tremendous strides in our understanding of the natural history of type 1 diabetes, most immunotherapeutic approaches to preventing and interdicting the disease process have been disappointing. Future 'cocktail' approaches will likely employ a combination of agents aimed at immunosuppressing and/or immunomodulating the destructive autoimmune response while at the same time preserving and/or regenerating beta cells. Traditional cellular sources have aimed at replacement of beta cells by whole organ or islet transplantation. Although studies are in their infancy, embryonic stem cells have the potential to differentiate and make insulin. Additionally, stem cells derived from cord blood, bone marrow, and even peripheral blood may trans differentiate into insulin-producing cells, stimulate pancreatic regeneration, or potentially restore immune tolerance through the action of mesenchymal stem cells, dendritic and/or regulatory T cells (CD4/CD25/FOXP3). Recently, short term efficacy using autologous 'nonmyeloablative' hematopoietic stem cell transplantation was reported. The morbidity and potential mortality associated with using such an approach will likely limit wide spread applicability. Exploratory efficacy, safety, and mechanistic studies are currently underway using autologous cord blood, dendritic cells and mesenchymal stem cells to ameliorate the disease process.

INV10

Acceleration: concept or reality?

T. Wilkin

Endocrinology and Metabolism, Peninsula Medical School, Plymouth, UK

Diabetes is a disorder of beta cell insufficiency. Insulin resistance imposes the biggest strain on insulin sufficiency, and the Accelerator Hypothesis proposes that type 1 and type 2 diabetes

are the same disorder of insulin resistance, set against different genetic backgrounds. Insulin resistance is largely attributable to mounting obesity, and it up-regulates beta cells, which apoptose faster as a result. Type 2 diabetes, once a disorder of middle-age and beyond, now presents in childhood. A small minority carry immune response (HLA) genes that react intensely to up-regulation, further accelerating beta cell loss. Type 1 diabetes, once a disorder of puberty and adolescence, is now rising fastest in the under fives. What is the evidence that beta cell loss is accelerated by childhood obesity? We have plotted changing disposition in the EarlyBird cohort over time from 5 to 12 years in 307 healthy children (EarlyBird study), using HOMA measures of insulin sensitivity (%IS) and beta cell reserve (%B). The trajectories of the most insulin sensitive and least insulin sensitive quartiles were very different. %B fell and glucose rose in the least insulin sensitive, suggesting that one was a cause of the other. There was a predictable and compensatory rise in insulin sensitivity, but it was short-lived, and the trajectory underwent a sharp inflexion at around 8 year. The most insulin sensitive, on the other hand, showed no such fall in %B, and no inflexion. The inflexion may be a critical event in the decline of beta cell function. Vector plotting is beginning to reveal in 'healthy' children the earliest acceleration of beta cell loss, and may offer a better understanding of where to target prevention. What lies behind childhood obesity? We have analyzed the relationships in BMI in EarlyBird trios. The BMI's of daughters of obese mothers were 1.39 SD higher than the BMI's of daughters of normal weight mothers ($p < 0.001$), the greatest effect size we have so far seen in childhood obesity, and the corresponding difference for sons and fathers was 1.20 SD. Same-sex offspring of normal weight parents were no heavier than the average child of 25 years ago. Without obese/overweight mothers, the prevalence of obesity in girls of 8 year would fall from 37% to 5%. Same-sex transmission is more likely to be behavioral than genetic. In conclusion, beta cell loss appears to occur early in life, restricted to children who are insulin resistant. Obesity is a major contributor to insulin resistance and same-sex obesity in the parent is a major contributor to childhood obesity. Parents may be the important target in the prevention of childhood diabetes.

INV11

Primary prevention of T1D-environmental approaches

D. Becker

Children's Hospital of UPMC, Pediatric Endocrinology, Diabetes Mellitus and Metabolism, Pittsburgh, PA, USA

Although the role of HLA genes in mediating the autoimmune destruction of insulin-producing beta cells is irrefutable, the lack of concordance of clinical diabetes amongst identical twins is an example of the role of environmental influences in T1D. Numerous epidemiologic studies have demonstrated associations between the incidence of T1D or the development of autoantibodies, and prenatal or postnatal viral infections, nutrients in the diet including cow milk and gluten, Vit D and childhood growth rate. However, results from these association studies are controversial and not always reproducible. This is not surprising as it is extremely difficult to assess the role of ubiquitous environmental factors in the etiology of disease. Manipulation of the environment and a number of nutritional factors have been shown to be effective in disease prevention in diabetes prone rodent models. There is increasing interest in the possibility that abnormalities in the gut mucosal barrier may determine the initiation of autoimmunity. The role of environmental factors in humans is suggested by the effects of a number of dietary nutrients and

specific viral and nutrient epitopes on T-cell function in humans with diabetes compared to controls. Larger epidemiologic and intervention studies are needed to assess the role of environmental factors and their manipulation in the prevention of T1D. To date, there have been two completed nutrition pilot studies and others recently initiated. The first pilot study for the primary prevention of the development of autoantibodies to islet cells was completed in Finland which suggested that the substitution of a hydrolyzed protein formula for a regular cow milk formula may decrease the development of islet autoantibodies and possibly type 1 diabetes. These promising data led to the development of the international TRIGR study (Trial to Reduce Insulin Dependent Diabetes in the Genetically At-Risk) which will have completed enrollment at the end of 2006. Neither a small primary nor a small secondary prevention pilot study assessing the effect of the elimination of gluten from the diet demonstrated any beneficial effect on preservation of beta cell function or the development of autoantibodies. Pilot trials of the effect of the addition of a poly-unsaturated fatty acid (DHA) to formula and oral insulin in high risk newborns are underway. Protocol development to test the effectiveness of high dose of vitamin D is also underway. To date, there are no intervention trials related to viral infections. A potential role of excess caloric intake associated with decreased activity and obesity with attendant insulin resistance, have been postulated to result in acceleration of either the autoimmune process or the clinical presentation of diabetes, accounting for the rising incidence in childhood T1D around the world. Intervention trials that might affect insulin sensitivity are under discussion. It is probable that numerous environmental factors play a role, possibly synergistically or in individuals with specific genotypes.

INV12

Status and rationale of reno-protection studies in adolescents with type 1 diabetes

D. B. Dunger

Professor of Paediatrics, Department of Paediatrics University of Cambridge, Cambridge, UK

Adolescence is a particularly vulnerable period for the development of microangiopathic complications of diabetes. Glycaemic control invariably deteriorates and the hormonal changes of puberty may be independent determinants of risk for microalbuminuria – an established marker for later cardiovascular and nephropathy risk. The development of microalbuminuria is a marker of a generalized endotheliopathy which is characterised by changes in flow-mediated vascular dilation and carotid artery intima medial thickness, changes in inflammatory markers such as hsCRP, hypoglycaemia and decline in glomerular function. Although screening for microalbuminuria is currently advised through ISPAD guidelines there is no consensus as to how it should be managed. Interventions with ACE inhibitors and statins are well established in adults with type 1 diabetes but this approach has not been evaluated during adolescence. Microalbuminuria represents an arbitrary cut off and consistent increases in albumin excretion within the normal range may also be predictive of complications risk. Risk associated with rising albumin excretion during adolescence will be used to define high risk subjects from the adolescent population for an international multi-centre placebo-controlled trial of ACE inhibitors and statins funded by the JDRF, Diabetes UK, the BHF and Pfizer which is currently recruiting patients throughout the UK, Canada and Australia. This study will determine whether the potential cardio-renal protection afforded by these drugs will reverse long term risk for diabetic nephropathy and cardiovascular disease in this vulnerable adolescent population.

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INV13

Nicotine, alcohol, marijuana and other substance abuse vis-à-vis pediatric and adolescent diabetes 2008

S. J. Brink

New England Diabetes and Endocrinology Center and Tufts University School of Medicine, Waltham and Boston, MA, USA

Experimentation may start as early as 9 or 10 years old. No reason to believe that children/adolescents with diabetes will be much different than their peers without diabetes re: experimentation with smoking, alcohol, marijuana or other drugs. Confidential issues, societal issues, moralistic issues are all critical for health care providers to consider. Challenging behavior is less important than providing empowerment and discussion potential. Nonjudgmental discourse sets the stage for later questions, introspection, promoting self-esteem, encouraging individual rather than peer-pressured decisions. Family history an important factor to consider. When no scientific evidence, utilize SBGM to allow individual learning (...what happens to you?). Social learning hypothesis of Bandura and Sheffield/McGuire theory of psychological inoculation useful for understanding such common social behaviors as smoking, alcohol and marijuana use and also possible prevention/intervention strategies. Ensure general information about specific choices are known to patients and then make diabetes-specific information available in an ongoing fashion vis-à-vis driving, cognition, appetite change, somnolence, euphoria, hyperglycemia as well as hypoglycemia. Consider strategies as alternative approaches, role-playing and ongoing discussions according to self-esteem, depression and anxiety issues, family issues and known other risk factors (ie. school performance, PTSD, learning problems etc) requiring more specific psychosocial intervention and therapy.

INV14

Screening for psychosocial problems in type 1 diabetes

E. Northam

Department of Psychology, Mental Health Service, Royal Children's Hospital, Parkville, Australia

Empirical and epidemiological research has shown that psychological morbidity is increased in children with type 1 diabetes. Psychological maladjustment is of particular concern in this population as it is associated with an increased risk of metabolic control difficulties. These data pose challenges for clinicians caring for young people with T1DM. Not all children require mental health services, nor would it be cost effective or feasible to provide them, hence it is important to identify specific risk and protective factors that influence this dual morbidity. Clinic populations could then be screened early in the course of the illness and interventions targeted to those who actually need them. The second imperative is to identify effective interventions for use with children with T1DM "at risk" for adverse mental and physical health outcomes. An effective intervention should be theory driven, based on empirical findings, have clearly articulated, preferably standardized protocols to facilitate evaluation and replication and have high feasibility for inclusion in comprehensive health care. Review of the intervention literature (1) suggests that psychosocial interventions in pediatric T1DM to date have been compromised by methodological deficiencies and a focus on changing diabetes-specific behaviors rather than addressing underlying psychological symptoms that may contribute to non-adherent behaviors. This paper will outline proposed screening and intervention strategies to be trialed in a large, tertiary hospital-based pediatric T1DM clinic. outlined.

Reference:

1. Northam EA, Todd S and Cameron FJ. Interventions to promote optimal health outcomes in children with type 1 diabetes - are they effective? *Diabetic Medicine* 2006, 23:113–21.

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INV15

Risk-taking behavior in diabetes

A. M. Delamater

University of Miami, Miami, FL, USA

This paper will discuss risk taking behavior in youth with diabetes, but will not address traditional “risky” behaviors such as tobacco, drug and alcohol use, and unprotected sexual activity, covered by another speaker in this symposium. Rather, the focus will be on behaviors that place the youth at metabolic risk via non-adherence to prescribed regimens. These behaviors may be construed as being either inadvertent or volitional non-adherence. Inadvertent non-adherence assumes the patient and family accept the regimen but may not have been properly educated, may not recognize non-adherence as problematic, or may simply forget the treatment and not appreciate its significance; volitional non-adherence implies deliberate, voluntary behavior inconsistent with optimal diabetes management. Volitional non-adherence is a helpful conceptual approach to the problem of non-adherence, allowing an understanding of non-adherence in the context of complex decision-making and the patient-physician relationship. Non-adherence may be adaptive or non-adaptive: it can sometimes make sense, and is not necessarily deviant, when patients and their families experiment with their regimen. Seen from this perspective, non-adherence is a common phenomenon, and makes sense given that patients and their parents are essentially “in charge” of their own treatment. To the extent that non-adherence is a conscious decision, understanding how patients make these decisions can lead to more effective work with them. However, not all non-adherence is volitional in the sense that it is the result of rational decision-making to consciously modify the treatment regimen, and as such may increase risk for metabolic control problems. Besides lack of understanding of the treatment regimen, psychosocial factors such as family conflict, diffusion of responsibilities for regimen tasks, and psychosocial problems (including adjustment difficulties, maladaptive coping, depression, and eating disorders) all may increase the likelihood of inadequate self care behaviors and metabolic control problems. Topics that will be covered include falsification of blood glucose monitoring records, insulin omission, binge and secretive eating, and lack of parental involvement in the regimen. Special concerns for adolescents, including driving automobiles and engaging in unprotected sex will also be considered. Recommendations for clinical practice and future research will be discussed.

INV16

Preventing hypoglycemia

W. L. Clarke & R. M. Blizzard

University of Virginia, Virginia, USA

Hypoglycemia remains the major barrier to the achievement of near normal blood glucose (BG) levels in persons with type 1 diabetes. Its occurrence is frequent, frightening, and often unpredictable. In order to prevent its occurrence, it is important to understand the biopsychophysiology steps in the generation of severe hypoglycemia. Treatment regimens and the balancing of insulin, food, and physical activity determine the BG level. A low BG (< 70 mg/dl [3.9 mmol]) can suppress adrenergic symptoms and lead to subsequent low BG within the next 24 hours, an event often characterized by an even lower BG. Our research team has used “risk analysis” to develop the Low Blood Glucose Index, which is calculated using SMBG determinations and which can predict future (within 6 months.) and imminent (within 24–48 hours) hypoglycemia. Physical symptoms of low BG include glucose counter-regulation and neuroglycopenia. Glucose counter-regulation can be suppressed by frequent low BG events;

“Hypoglycemia Associated Autonomic Failure”, Low BG symptoms may differ in children and in adults and recognition of these symptoms and their usefulness as clues to low BG detection must be taught to patients and their families. Competing activities can influence judgment to treat low BG, even when it is accurately detected. Our research team has shown that children (6–12 years) and their parents are very inaccurate at symptom recognition and BG estimation. Treatment of low BG must include an appropriate rapid acting carbohydrate and should never be delayed. Parents are especially concerned with nocturnal hypoglycemia and strategies have evolved for reducing its frequency. The development of continuous glucose sensors (CGS) holds the promise for early detection and prevention of hypoglycemia. The three commercially available (in the US) sensors are described along with their individual sensitivities to detect low BG and their “false positive” alarm rates. Unique to CGS is the determination of rate and direction of BG change. Such information can dramatically improve the accuracy of low BG detection. Indeed time spent in hypoglycemia is markedly reduced by those using any of the three CGS. Unfortunately nocturnal CGS hypoglycemia alarms are frequently not heard or ignored. Thus, as closed loop (artificial pancreas) systems are designed, a special effort is being made to prevent nocturnal hypoglycemia. Data on current prototypes and their ability to predict imminent hypoglycemia and prevent its occurrence will be presented.

INV17

Teaching strategies for initiating CSII

R. Hanas

Department of Pediatrics, Uddevalla Hospital, Uddevalla, Sweden

Possible indications for the use of CSII include high HbA1c, high blood glucose during the night, dawn phenomenon, recurrent severe hypoglycemia, patients prone to ketosis, unstable blood glucose, irregular eating patterns, missed injections, eating disorders, pain from insulin or needle and life quality benefits. Lack of insulin due to missed injections is one of the most common reasons for a high HbA1c. An adolescent who ‘forgets’ many or most of the injections will often do much better on a pump that at least supplies the basal insulin regularly. Older children and teenagers attend the day care unit for 3 days for pump initiation. Many pre-school children < 5 years are started on a pump at the onset of diabetes. Younger children (< 3–4 years of age) are admitted to the hospital for one to two nights, and are then followed up at the day care unit. During the initial phase we require blood glucose measurements before and 1.5–2 hours after each meal, plus one to two night time tests. Our instructions to patients on pumps are to take preferably four to five blood glucose tests each day. Testing for ketones is mandatory if blood glucose is > 15mmol/l for more than a couple of hours, the patient is ill or is nauseous/vomiting. Some teenagers, however, find it difficult to achieve frequent monitoring; in fact, a small number of them take very few tests at all. As long as they do not have complications with recurrent severe hypoglycemia or ketoacidosis we usually let them keep the pump. In this patient group we find many of the higher HbA1c values, which without a pump would be even higher. Today we start all pumps on rapid-acting insulin analogs. Approximately 40–50% of the daily insulin requirement is given as basal rate. The remainder is given as pre-meal bolus doses. The total insulin requirement per 24 hours usually decreases 15–20% after starting with insulin pump treatment. We use 50 U/ml in younger children if the basal rate is < 0.3 U/hour and 10 U/ml in infants. We usually start the patient on five separate basal rate profiles; one in the early night, one in the late night/morning and one for each main meal. Prepubertal children often need the

highest basal rate between 9.00 PM and 12.00 AM and it is not uncommon for the basal rates to be higher earlier in the night (12.00–3.00 AM) than later on (3.00–7.00 AM). Standard advice is to decrease the basal rate during the night after physical exercise and to increase in case of intercurrent illness with rising blood glucose levels.

INV18

The role of the IDF in insulin procurement: the IDF task force on insulin availability and diabetes monitoring supplies

L. C. Deeb^{1,2}

¹Clinical Professor of Pediatrics, University of Florida College of Medicine, ²Clinical Professor of Medical Humanities and Social Sciences, Florida State University College of Medicine, FL, USA

The International Diabetes Federation (IDF) recognizes that the most common cause of death for children with diabetes is the lack of availability of insulin. As a member of the task force since 1991 and chair since 2006, we have sought ways to reduce this problem for people with diabetes. The needed changes in health care systems worldwide are difficult, but steady progress has been noted. IDF has made considerable progress in developing and implementing programs for emergencies worldwide. Donor partners and systems are in place to help provide insulin and testing supplies, often within hours to days of a disaster. During this triennium, the earthquake in Peru and the cyclone in Bangladesh are two examples of success. The TIDES initiative of IDF seeks to integrate with other first responders to disasters and help bring even better diabetes management to displaced people going forward. Discussions of the Life for a Child Program and the Insulin for Life Program are a part of the symposium and will be discussed in the context of the task force. This triennium, the Task Force has focused on two initiatives. Firstly, we are engaged in a survey of taxation and import duties on insulin. As an essential drug, defined by WHO, insulin should be available at the lowest possible cost. As data become available, IDF will direct attention to ministries of health in order to help reduce taxation and insulin price. The second initiative is the RAPIA, the rapid assessment of insulin availability. We have completed evaluations in Mali, Mozambique and Zambia in Africa as well as Nicaragua in the Americas. An assessment in Vietnam is just being completed. A yet to be selected country will be the focus of a 2009 assessment. Data from these assessments are used to make systematic changes and offer aid to countries in improving diabetes supplies.

INV19

The Year of the Child: the role of the IDF

G. Ogle

International Diabetes Federation Life for a Child Program, North Epping, Australia

The International Diabetes Federation (IDF) is an alliance of diabetes associations in over 160 countries that aims to advance the lives of people with diabetes everywhere. 2007–2008 and 2008–2009 have both been designated the Years of the Child. Much needs to be done: in the developing world many children with diabetes still die undiagnosed, or survive only a short time due to lack of insulin and skilled clinical

care. Others develop early and serious complications due to a shortage of insulin and lack of monitoring and education. Even in the developed world where comprehensive care is usually provided by the Government, children with diabetes still face many challenges and trials. The IDF's *Life for a Child* Program commenced in 2000 and now supports the care of almost 1000 children in 17 developing countries. Support is provided to recognised diabetes centres. Priority needs (insulin, syringes, monitoring, education) are determined, a budget defined, and a specific list of the most needy children are supported. The cost to support a child for a year is US\$200–400. The goal is to provide best-practice cost-effective care for that country. Health outcomes of the children, and financial trails are carefully monitored. By November 2009, we hope to increase the number of children assisted to 1500 or more. Partners include Diabetes Australia-NSW, HOPE *worldwide*, Insulin for Life, and Rotary International. Disbursed funds have grown from US\$12,276 in 2001 to a projected US\$170,000 in 2008. Some highlights include: country-wide approaches, implementation of self-monitoring, extension of support from capitals to provincial centres, provision of HbA1c testing, establishment of registers and clinical data collation, and recognition of children with type 2 diabetes. The IDF has also commenced a concerted effort to reduce the incidence of diabetic ketoacidosis in new-onset type 1 diabetes. Past education programs are being reviewed, and new strategies are being devised. Aside from these projects, the IDF's Consultative Sections on Youth and on Diabetes Education, as well as the Task Force on Insulin, Test Strips and Other Diabetes Supplies are involved in other initiatives that are benefitting children with diabetes.

INV20

Current controversies in pediatric diabetes

M. A. Sperling

Children's Hospital of Pittsburgh of UPMC, Pediatric Endocrinology, Pittsburgh, USA

Diabetes Mellitus is a complex syndrome caused by inadequate insulin secretion in relation to the prevailing degree of insulin sensitivity/resistance. At one extreme, near complete insulin deficiency (genetic or autoimmune) can never be compensated by even the most sensitive tissues; conversely total lack of insulin action (complete receptor/post receptor defects) can never be compensated by increased insulin secretion. Between these extremes, diabetes occurs when the product of insulin secretion x insulin sensitivity falls from its normal parabolic relation. From these postulates and its implications for etiology, biochemical disturbances, treatment options and their effect on complications, I review four current controversies in pediatric diabetes. (i) Type 1 DM and type 2 DM are each distinct entities and 'never the twain shall meet'. (ii) Cerebral edema can be prevented by appropriate and judicious use of fluids, electrolytes and insulin. (iii) Basal-bolus regimens using combinations of insulin analogs or programmable pumps are equivalent in their ability to achieve near optimal metabolic control, quality of life and avoidance of long-term complications. (iv) In selected cases, children, like adults, are appropriate candidates for islet transplantation or stem cell transplantation approaches for a cure. Finally, I broach the subject that barriers to effective diabetes care are largely are political/economic and require a concerted effort on the part of all ISPAD members to overcome this barrier throughout the world.

Invited Speakers

INV21

Hypoglycemia: the critical barrier limiting the pursuit and achievement of normoglycemia

J. Wolfsdorf

Children's Hospital Boston/Harvard Medical School, Medicine (Division of Endocrinology), Boston, MA, USA

Hypoglycemia is the most common acute complication of type 1 diabetes (T1D) treatment. Symptoms are unpleasant, disruptive, embarrassing; rarely, severe hypoglycemia (SH) causes permanent neurologic sequelae and death. Recurrent episodes cause hypoglycemia-associated autonomic failure: the clinical syndromes of defective glucose counterregulation and hypoglycemia unawareness. Hypoglycemia causes anxiety and fear in patients, parents and healthcare providers leading to deliberate insulin dose reductions and is a critical barrier limiting the pursuit and achievement of normoglycemia. Recently reported rates of SH (coma, seizures, glucagon or IV dextrose) are 16.6–36 events/100 patient-years. Risk of SH is increased with longer duration, age < 6 years, in adolescents, with lower HbA1c, higher insulin doses, lower parental socioeconomic status, psychiatric disorders, in adolescent males, and at diabetes centers with fewer patients. Up to 75% of SH episodes occur during the night. Nocturnal hypoglycemia (NH) is common (25–50%), often asymptomatic, prolonged, and disturbs sleep; its frequency doubles after exercise. NH is more common with a combination of evening regular and intermediate-acting insulins. Rapid- and long-acting insulin analogs or CSII reduces the risk of NH. Despite increased SH with intensive insulin therapy in the DCCT (adolescents 85.7 events/100 patient-years required assistance and 26.7 events/100 patient-years caused coma or seizure), SH did not cause worsening of neuropsychologic or cognitive functioning during the trial or up to 18 years after entry into the trial. In contrast, cognitive impairment attributed to recurrent SH has been well documented when T1D is diagnosed in early childhood. The effect of SH on long-term neuropsychologic functioning may be age-dependent, but the relationship between SH and CNS injury in children remains unclear. Other factors may adversely affect cognitive performance including short-term effects of recurrent hypoglycemia, adverse psychosocial effects of a chronic health condition, and chronic hyperglycemia in the very young child. In 15 years since the DCCT results mandated pursuit of normoglycemia as standard of care for T1D, advances in therapy have improved glycemic control and reduced the risk of SH in intensively treated children and adolescents. A closed-loop system that delivers insulin in response to real-time changes in glycemia is urgently needed to eliminate or further reduce the risk of SH.

INV22

Hypoglycemia – part villain, but not the only one

E. Northam

Royal Children's Hospital, Department of Psychology, Mental Health Service, Parkville, Australia

The central nervous system (CNS) is one of the organ systems affected in T1DM as both cerebral glucose and insulin levels are frequently abnormal, even when diabetes is well-controlled. Hypoglycaemia triggers a continuum of events, ranging from confusion through seizures and coma, and ultimately to death unless appropriate action is taken. Hyperglycaemia disrupts blood-brain barrier function, alters neurometabolite profiles and depresses cerebral blood flow acutely, while chronic poor control is associated with cerebrovascular disease and neuropathy. Hypo- or hyper-insulinemia may also

affect brain function, while the impact on the CNS of osmotic changes associated with constantly fluctuating glucose concentrations is unclear. There is a growing literature documenting pathophysiological and neurocognitive changes in T1DM patients but causal relationships between specific illness variables and CNS changes are still debated. In adults, CNS effects have been linked most consistently with longer duration of disease and secondary complications associated with chronic hyperglycaemia. In children, the focus has traditionally been on the neurotoxic effects of severe hypoglycaemia, particularly in very young children at an early stage of brain development. Inconsistent empirical findings have led to this hypothesis being challenged, with Ryan (1) arguing that it is chronic hyperglycaemia that disrupts normal brain development, increasing the child's vulnerability to subsequent brain insults, including severe hypoglycaemia. To date, methodological issues have complicated our understanding of the pathophysiological pathways to CNS damage in T1DM. Reliable and complete ascertainment of metabolic control history is problematic even in prospective research. Individual patients may have more than one putative risk factor, leading to unacceptable levels of multi-collinearity between predictor variables in regression analyses. Very large, probably multi-centre, samples would be required to form discrete subgroups of patients with a single risk factor. Furthermore, research to date has been descriptive rather than testing a specific hypothesis. This paper will argue that it is premature to dismiss the possibility of hypoglycaemia-mediated brain damage in early-onset T1DM. To improve understanding of the risk factors for CNS damage in T1DM, future research should use more sophisticated models in hypothesis driven studies, testing for additive and synergistic effects between risk factors as well as interactions with critical periods of neurodevelopment.

Reference:

1. Ryan CM. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. *Pediatr Diabetes* 2006, 7: 289–97.

INV23

And the real villain is...hyperglycemia and the development of neurocognitive dysfunction in children and adolescents

C. Ryan

University of Pittsburgh School of Medicine, Psychiatry, Pittsburgh, USA

Regardless of age, individuals with either type 1 or type 2 diabetes mellitus manifest an array of modest functional and structural changes within the CNS. Performance on measures of intelligence and mental efficiency is somewhat poorer, cerebral blood flow is altered, neural slowing is evident, and gray matter density is reduced. These changes occur relatively early in the course of the disease, do not appear to be progressive over time (unless one develops significant microvascular complications), and are correlated not with recurrent episodes of moderately severe hypoglycemia, but with indicators of poorer metabolic control. Following a brief review of the recent literature supporting those statements, I explore several different ways of thinking about 'glucose neurotoxicity,' speculate on how these mechanisms could affect the development of CNS changes during different stages of childhood and adolescence, and discuss the remarkable resilience of the brain to both hypo- and hyperglycemic insults.