Pediatric Diabetes 2008: 9: 3–8
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Pediatric Diabetes

Review Article

Diabetes in motion in the year of the child. Meeting Highlights – 33rd Annual ISPAD Meeting, September 26–29, 2007, Berlin, Germany – 5th Symposium on Diabetic Angiopathy in Children, September 30, 2007, Berlin, Germany

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Key words: adolescent – child – diabetes mellitus – infant – research

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Submitted 15 October 2007. Accepted for publication 19 October 2007

The 33rd Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD) was held 26–30 September 2007 and was entitled 'Diabetes in Motion in the Year of the Child'. This title reflects the rapidly changing clinical care and research in the field of pediatric diabetes and the recognition given by the United Nations dedicating the inaugural World Diabetes Day to children. It also encouraged recognition of the unique and changing needs of children and adolescents with diabetes and their families as these 'moving targets' progress through different developmental stages from infancy to transition to adult care. Therefore, it was appropriate that this year's meeting was held in Berlin, Germany, a city that has also been 'in motion' with reunification and redevelopment.

With over 1300 participants from 66 countries representing all regions of the world, it was the largest ISPAD meeting in the history of the society. Thirty percent of the participants were non-physicians, reflecting the importance that ISPAD places on the role of multidisciplinary teams in the care of young people with diabetes. The participants appreciated the excellent basic clinical program developed by the Conference President, Dr Olga Kordonouri and the local organizing committee consisting of Barbel Aschemeier, Walter Burger, Dorothee Deiss, Holger Haberland, Matthias Herr, Wieland Kiess, Karin Lange, and Renate Lauterborn.

The inaugural lecture was given by Prof. Edwin Gale (Bristol, UK), who proposed that the earlier onset of immune-mediated diabetes is related to a more affluent human phenotype. He described several potential environmental accelerators such as earlier puberty, increased maternal age, loss of 'immune educators', known as the *Hygiene hypothesis*, increased obesity, and insulin resistance. He also proposed that there was no clear dividing line between type 1 diabetes (T1D) and type 2 diabetes (T2D) and suggested to consider them as different in their *degree rather than in their nature*. Prof. Terry Wilkin (Plymouth, UK) also described a similar concept, the *Accelerator hypothesis* (1), which considers that insulin resistance and genetic susceptibility interact to define the age of onset of diabetes (2).

The plenary session 'Genes & Environment: New Approaches to Prevention' addressed developments aiming to restore insulin secretion. Dr Anette Ziegler from Hospital München-Schwabing, Germany, described how patients who are C-peptide positive have better metabolic control and exhibit a lower frequency of hypoglycemia compared with those without any endogenous insulin secretion. Dr Ziegler described that treatment with anti-CD3 antibodies in patients with recent onset of T1D may improve insulin secretion at 18-month follow-up (3). Dr Catarina Limbert, from the University of Würzburg (Germany), presented promising data about adult stem cells. She described that adult stem cells obtained from bone marrow tissue have been able to develop markers of insulin synthesis and even store and secrete some insulin. In an oral presentation, Dr Limbert also described that introduction of key endocrine pancreatic transcription factors into human bone marrow-derived mesenchymal stem cells enabled differentiation toward an insulin-producing phenotype (4). Several other abstracts also evaluated aspects of islet cell molecular biology (5, 6).

The third speaker of this session, Dr Massimo Trucco, from the Children's Hospital of Pittsburgh, USA, described new protocols aiming to stimulate regeneration of the remaining β-cells in the recently diagnosed patient. He postulated that simultaneous elimination of ongoing pancreatic autoimmunity and avoidance of hyperglycemia by insulin treatment would allow β cells to express their own regenerative capacity. He referred to several different ways that have been used to abrogate insulin autoimmunity such as intradermal administration of autologous diabetes-suppressive dendritic cells and the transplant of autologous non-myeloablative hematopoietic stem cells (7).

A symposium was held regarding new strategies for prevention of T1D. Administration of probiotics was addressed by Dr Outi Vaarala (Helsinki, Finland), who reported that oral administration of heat-killed *Lactobacillus casei* has decreased the incidence of diabetes in non-obese diabetic (NOD) mice. Dr Vaarala described the PRODIA study, which is evaluating the administration of probiotics to infants at genetic risk of developing T1D prevents β-cell autoimmunity.

Vitamin D could be another possible agent for prevention of T1D. Prof. Klaus Badenhoop, Frankfurt, Germany, provided an overview of vitamin D metabolism and its pleiotropic cellular effects. Vitamin D has been proposed to have a role in β-cell protection. Vitamin D deficiency has been observed in cohorts of patients with T1D (8–10). However, genetic factors may also need to be considered (11–14). In NOD mice, activated vitamin D3 and new non-calcemic analogs have been reported to diminish diabetes onset (15). Clinical studies assessing high-dose vitamin D treatment in subjects at high risk of T1D are under development.

Dr Constantine Polychronakos (Montreal, Canada) addressed the topic of 'Genes and T2D'. Candidate gene approaches have identified T2D susceptibility loci, including the transcription factor TCF7L2 and the β-cell potassium channel Kir6.2. The speaker then reported that recent genome-wide association studies have led to the identification of several additional T2D loci such as SLC30A8, a β-cell-specific zinc transporter, and HHEX, a gene involved in pancreas development (16). He predicted that all important T2D loci will be known within 2–3 yr.

Dr C. Mantzoros (Boston, MA, USA) and Dr S Blüher (Leipzig, Germany) discussed the nature of adipose tissue as an endocrine organ and provided comprehensive overviews of the current knowledge about adipokines and their applications to clinical practice. Clinical applications of leptin administration in several conditions are emerging, e.g., congenital leptin deficiency, hypothalamic amenorrhea, and lipoatrophic disorders (17). They also reviewed the clinical importance of adiponectin and other new molecules such as visfatin, omentin, apelin, and serum retinol-binding protein.

The joint European Diabetes Prospective Complications Study Group (EURODIAB)/ISPAD symposium was titled 'Recent trends in Epidemiology'. Dr C. Patterson, on behalf of the EURODIAB, described

a continuous increase in the incidence of T1D in children, especially in those younger than 5 yr, and a higher rate of increase in those countries with a lower rate of diabetes, such as east and central Europe. As pointed out by Dr Gyula Soltesz from the University of Pécs, Hungary, T1D is still the main form of diabetes observed in the young population. Maturity onset diabetes of the young (MODY) and T2D are the main non-T1D observed in most centers. However, there are no good registries of non-T1D.

Promising data regarding the epidemiology of nephropathy were presented by Dr Giselle Dahlquist, Umeå University, Sweden. She showed that a decrease in diabetes-related end-stage renal disease is being observed in diabetes centers and also in population-based studies. However, a strong geographic variation occurs within Europe.

At the International Diabetes Federation (IDF)/ ISPAD joint symposium, Drs Julie Edge (Oxford, UK), Maurizio Vanelli (Parma, Italy), and Andreas Neu (Tübingen, Germany) reviewed the global epidemiology of diabetic ketoacidosis (DKA) and issues relating to prevention of DKA at diagnosis. In addition to global access to insulin, the speakers highlighted the importance of educating physicians in the primary care setting for early detection of diabetes, exemplified by the Parma campaign (18, 19).

A third joint symposium was sponsored by European Society of Pediatric Endocrinology (ESPE)/ISPAD and dedicated to 'Diabetes and Puberty: Mechanistic Views'. Prof. David Dunger, Cambridge, UK, described how boys with T1D exhibit lower androgen levels during puberty and a delay of pubertal events. Similarly, he described the presence of lower adrenal androgens during adrenarche in girls. However, females later in life present with higher levels of androgens and elevated rates of polycystic ovarian syndrome (20). Dr Dunger showed data from a longitudinal cohort demonstrating that higher androgen levels are associated with a higher risk of microalbuminuria (21) and preliminary data about the use of metformin–flutamide treatment of hyperandrogenic adolescent girls (22).

Dr Ethel Codner, from the University of Chile, described how physiologic estrogen levels are important in maintaining normal insulin sensitivity and secretion in adult women. In addition, estrogens have been shown to protect β cells from oxidative damage and apoptosis in mice. In pubertal girls with T1D, a delay in the final steps of puberty has been observed (23, 24), with a mild decrease in the observed estrogen levels that may be associated with the elevated rate of metabolic derangements observed in girls during this stage (25).

Prof. Sylva Arslanian, Children's Hospital of Pittsburgh, USA, described how insulin resistance of puberty results in a decreased response to insulin of glucose, lipid, and protein metabolism. She emphasized that these physiologic changes are beneficial when occurring in a healthy subject but becomes a pathogenic condition when insulin resistance of puberty is pathologically exacerbated, such as in states of obesity or T1D.

The Lestradet Award and lecture to an outstanding educator in diabetes was given to Margaret McGill from the Royal Prince Alfred Hospital, Sydney, Australia. She described her 'wonderful journey in diabetes education,' the importance of developing a cultural appropriate diabetes education program and the role of the diabetes team.

Following the Lestradet lecture, Dr Barbara Anderson (Texas, TX, USA) described the stimulating results of a family-focused therapy performed within the context of the diabetes clinic. She described a program of short counseling sessions aimed to prevent the natural decline in parental involvement in diabetes care observed over time, the diabetes care burnout, and the increase in conflict that usually occurs in families who take care of a child with T1D. Psychosocial issues were also addressed in oral and poster sessions. Maartje de Wit (Amsterdam, the Netherlands) received the Best Oral Award for a study, which demonstrated that monitoring health-related quality of life in adolescents with T1D improves psychosocial health and satisfaction with care (26).

One of the highlights of the meeting was the 'Young Investigators Award'; this prize was given for the second time by ISPAD. Dr Helge Rædels from the University of Bergen in Norway described his research regarding cross talk between the endocrine and exocrine pancreas. This included his findings of a new form of MODY, called MODY8 (OMIM#609812), caused by a mutation in the carboxyl ester lipase gene (27, 28), which involves endocrine and exocrine pancreatic insufficiency because of early lipomatosis of the pancreas. In addition, Dr Rædel described the frequent association of endocrine abnormalities in exocrine pancreatic diseases such as cystic fibrosis, pancreatitis, and pancreatic cancer. He postulated that this association may be explained by the local release of inflammatory cytokines or by the presence of undernutrition.

Another highlight was the 'Prize for Achievement' for extensive contributions in the field of pediatric diabetes. This year, this award was given to Dr Teruo Kitagawa, Tokyo, Japan, for his diabetes screening programs and characterization of childhood T2D in Japan (29).

During the symposium entitled 'Great Beginnings: Neonatal Origins of Later Diabetes', Dr Jörg Dötsch from University of Erlange, Germany, described how perinatal programming causes permanent fixation of temporary metabolic changes in the fetus and neonate, leading to pathological consequences later in life. He described how this process may be related to lower levels of leptin in the growth-restricted neonate, leading to defective development of neurons in the

hypothalamus of the young child (30). In addition, the process of programming continues after birth and the magnitude of weight gain during infancy also has an effect on the programming process. Of great interest were the new findings of a relationship of intra-uterine growth restriction in mice and the appearance of signs of glomerulosclerosis and IgA nephropathy later in life. During this symposium, Dr Claire Lévy-Marchal, from the Robert Debré Hospital and INSERM, Paris, France, reported results of the Haguenau cohort, a community-based population followed for more than 30 yr. She showed that the earliest observed alteration in the small for gestational age-group was a very early onset of increased fat mass. However, she emphasized that the abnormalities observed in some subjects born small for gestational age (SGA) are of modest magnitude, but may be amplified by other factors.

A workshop was conducted by Prof. Johnny Ludvigsson (Linköping, Sweden), Dr Sheridan Waldron (Leicester, UK), and Renate Lauterborn (Berlin, Germany) to address the issue *Is Carbohydrate Counting Essential for Successful Treatment?* Different opinions and approaches currently exist, and this remains a controversial issue indicated by the extensive discussion generated. Attention was drawn to the recently published ISPAD Clinical Practice Consensus Guidelines on nutrition management (31). During the workshop, the importance of individualized education/approach was emphasized, in addition to consideration of psychosocial factors, recognizing that food issues are common reasons for family conflict and there is a high incidence of disturbed eating behavior in youth with T1D (32). A poster presentation by Dr Carmel Smart (Newcastle, Australia) concluded that children on intensive insulin therapy only need to count to 10 g carbohydrate portions to maintain adequate glycemic control (33). Rochelle Ryan from Newcastle, Australia, received the Best Poster Prize for a study that identified that glycemic index and preprandial insulin administration have a greater influence than insulin type on postprandial glucose levels (34).

The 'Loop Club' workshop addressed the importance of glucose variability in the care of T1D. Dr Moshe Phillip (Petah Tikva, Israel) referred to the lack of correlation between glycemic variations in the Diabetes Control and Complications Trial (DCCT) cohort and microvascular complications (35). However, with modern technology, new measures of glucose variability are available and minimizing this may have other benefits such as decreasing the frequency of hypoglycemia. Dr Dorothee Deiss (Charité Children's Hospital, Berlin, Germany) discussed strategies to minimize glucose variability such as insulin management algorithms, real-time continuous glucose monitoring, and computerized algorithms.

The new ISPAD Consensus Guidelines were discussed. Dr Joseph Wolfsdorf, from Harvard University, USA, described the recent ketoacidosis recommendations endorsed by ISPAD, ESPE, and Lawson Wilkins Pediatric Endocrinology Society (36, 37). In addition, he referred to recent papers demonstrating beneficial effect of using isotonic fluids and avoiding insulin bolus in preventing cerebral edema (38, 39). These data confirm the ISPAD recommendation for DKA treatment.

Another issue discussed during the ISPAD Consensus Guidelines session was whether the desirable glycemic levels should vary with age. The members decided that there was not sufficient evidence to allow young children to have higher blood glucose levels and accepted, as a desirable goal, to have a similar hemoglobin A1c (HbA1c) in all age-groups. The audience voted for a target of HbA1c lower than 7.5%; however, some ISPAD members preferred a goal lower than 7% and a larger group voted for a cutoff of 8%. This point was discussed further the following day during the *5th Symposium on Diabetic Angiopathy in Children*. Dr Marion Rewers, Denver, CO, USA, argued that individualized goals, which take into account the age of the patient and several other factors, including having realistic expectations are preferred by the American and Canadian Diabetes Associations (40, 41). On the other hand, Dr Thomas Danne, Hanover, Germany, presented the European point of view of a strict goal of not higher than 7.5% for all children with diabetes.

The importance of metabolic control based on the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) studies was discussed by Neil White, St Louis, MO, USA. He presented new data from these studies showing that the intensively treated adolescent group, who showed a milder decrease in HbA1c than the adult patients (8.1 vs. 7.1%, respectively), did not exhibit the benefits of decreased complications after 10-yr follow-up, suggesting a lack of metabolic memory of a lower HbA1c over time in this population. However, statistical analysis showed that this lack of benefit over time was explained by the higher HbA1c in the adolescents compared with the adults, but not by age.

The *5th Symposium on Angiopathy in Children* also discussed the early recognition and early treatment of late complications of diabetes in childhood. Dr T. Reinehr (Datteln, Germany) addressed the risk of macroangiopathy in pediatric patients with diabetes and showed evidence of early vascular changes in children and adolescents with T1D and T2D. Prof. Denis Daneman from Toronto, Canada, outlined that multiple factors modify the risk of diabetic nephropathy, including genetic risk. He emphasized the key role of glycemic control and how psychosocial factors may also affect health outcomes (42). Longitudinal data from the Oxford Regional Prospective Study of Childhood Diabetes identified different albumin excretion

phenotypes in adolescents (43). Hence, prediction models for progression to guide early intervention may be feasible.

Dr Hans-Peter Hammes from Mannheim, Germany, outlined recent advances in the understanding of retinal vascular–cell interactions. Pericytes are important for endothelial cell survival, and their loss precedes the onset of retinopathy. A key mechanism is upregulation of angiopoietin-2. Hyperglycemia-induced reactive oxygen species are thought key to the pathogenesis of retinopathy (44). The contribution of glycemic variability, with glycemic excursions, may further augment oxidative stress (45). Therapeutic agents blocking the cellular mechanisms provoked by hyperglycemia are currently under development (e.g., thiamine derivatives/analogues and scavengers of reactive oxygen species).

Autonomic and peripheral neuropathy in pediatrics was discussed by Dr Kim Donoghue (Sydney, Australia). Dr Donoghue concluded that it is justified to consider both peripheral and autonomic neuropathy in children and adolescents with T1D because subclinical stages can be detected. Specific treatments are available, some experimental. She reviewed recent data showing that in addition to glycemic control, hypertension, and dyslipidaemia, obesity may be a risk factor for neuropathy (46, 47).

The 34th Annual ISPAD Meeting, entitled 'Advancing Diabetes Care' will be held from 13–16 August 2008 in Durban, South Africa. In the words of the Conference President Dr Kuben Pillay, *ISPAD has taken the visionary and courageous step of holding the next ISPAD annual meeting in a developing country for the first time. It is time to convert the political gains made into improving and advancing the care of children with diabetes throughout the world.* This will be an exciting opportunity to discuss advances in basic research and clinic care while networking with colleagues and friends in the ISPAD 'family'.

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