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Review Article

Highlights of the 34th annual ISPAD meeting, 13–16 August 2008, Durban, South Africa

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The 34th annual meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD), held in Durban, South Africa, was entitled 'Advancing Diabetes Care' and was aimed at reflecting the need for continuous improvement in care for the world's children with diabetes.

In his opening remarks, conference president Dr Kuben Pillay defined the magnitude of the problem of diabetes in the world today: currently, there are 440 000 children aged 0–14 yr with type 1 diabetes mellitus (T1DM) all over the world with a 3% annual increase and estimated number of 70 000 newly diagnosed cases per year (www.df.org/e-atlas). A series of short videos shown throughout the conference reinforced our need to strive for a better world for youth with diabetes. Dr Stuart Brink, Boston, MA, USA, the outgoing ISPAD president, highlighted the initiatives achieved during the 'Year of The Child': the United Nations Youth Ambassador programme and the International Diabetes Federation (IDFs) Life for a Child programme. The second year of the child will focus on decreasing diabetic ketoacidosis (DKA) at presentation – based upon the successful Parma project (1).

In the opening plenary lecture, Dr Denis Daneman, Toronto, Canada, addressed the state of the world's children with diabetes, highlighting that health outcomes of children with diabetes can be linked to the five domains of the Ecological Perspectives Model, namely societal, community, institutional, inter- and intrapersonal (2, 3). He proposed that outcomes of children with T1DM depend on the macro- and microenvironments in which they 'find' themselves, highlighting the different health care burdens and priorities between the developing and the developed world. The single most common cause of death from diabetes in childhood remains lack of access to sufficient supplies of insulin. Support for children with diabetes ought to be a collaborative effort between national governments of developing and developed countries, non-governmental organizations and industry.

Several speakers addressed the macroenvironmental factors: Dr Anju Virmani, New Delhi, India, discussed the extreme poverty ratio of 22% in India as a significant confounder of diabetes care. Its causes are discriminatory social milieu; illiteracy; unqualified public health systems; frequent misdiagnosis of diabetes; the unavailability of syringes, glucose and urine test strips; the inappropriate handling of insulin at extremes of temperature (cold chain failure); intermittent insulin deprivation and poor nourishment adding to poorer chronic illness control and an inability to leave the poverty cycle.

Dr Erick Richmond, San Jose, Costa Rica, presented the experience of diabetes care in a third world economy, with 95% literacy, 6% unemployment, but only

one pediatric diabetes centre and qualified team attending all new-onset patients. Incidence rate in Costa Rica is 3.5/100 000, 50% DKA at diagnosis, 95% are treated with non-analogue insulins.

Dr Thomas Danne, Hannover, Germany, discussed the goals of diabetes care, suggesting that benchmarking is a key to success and demonstrating that clear and consistent setting of goals is associated with a better outcome, as practiced in his centre, with 50% reaching haemoglobin A1c (HbA1c) goal <7.5%. A higher HbA1c in the first year of diabetes is associated with a higher risk of early development of retinopathy (4). He emphasized the newly emerging goals of therapy, such as quality of life (QoL) (5) and glycaemic variability (6). He concluded that children with diabetes need age-appropriate education for good QoL by a dedicated qualified team (SWEET project) (www.sweet-project.eu).

The joint IDF and ISPAD plenary symposium addressed the role of macroenvironmental intervention. Dr Rosangela Rea, Parana, Brazil, advocated the application of 'a youth charter' to detect the key specific challenges of disease burden and organize comprehensive strategies for systemic improvement. Dr Larry Deeb, Tallahassee, FL, USA, and Dr Graham Ogle, North Epping, Australia, focused on the role of the IDF in preventing youth death of diabetes, recognizing that the most common cause of death is lack of insulin availability. Nearly one-third of diabetic youth are located in low-income areas with life expectancy as short as 7 months to 3 yr once diabetes has been diagnosed. The IDF is involved in several initiatives: Task force for immediate availability of monitoring supplies and insulin worldwide during emergencies, contribution to changes in health care systems, reduction of taxation and insulin price.

The contribution and further benefit of ISPAD Guidelines worldwide in various macroenvironmental settings was discussed by Dr Kandi Muze, Dares Salaam, Tanzania; Dr Amina Balafrej, Rabat, Morocco, and Dr Fauzia Mohsin, Dhaka, Bangladesh, and chaired by Dr Ragnar Hanas, Uddevalla, Sweden, and Dr Peter Swift, Leicester, UK. Extreme poverty, lack of education, lack of an adequately educated health care team, lack of equipment and insulin and the lack of involvement and responsibility of the government lead to practical inability to follow the treatment according to the ISPAD guidelines, especially regarding DKA treatment.

Microenvironmental factors affecting diabetes care were discussed during the Psycho-Social issues symposium; the Diabetes Care, Education and Psycho-Social session and several workshops.

Dr Liz Northam, Parkville, Australia, presented data to show that psychological morbidity is increased in children with T1DM, especially anxiety and mood disorders; therefore, team screening for these disorders is imperative in cases of family history or poor metabolic control. Mental health services are required, although interventions today mainly focus on changing diabetes-specific behaviours rather than addressing underlying psychological symptoms (7, 8). Dr Marcia Frank, Toronto, Canada, suggested that psychosocial interventions may have a modest effect on metabolic control and QoL but most effective when integrated into routine care, parents are involved and self-efficacy is promoted. Suggested effective interventions are the following: coping skills training, behaviour family system therapy and motivational interviewing (9, 10).

Dr Alan Delamater, Miami, FL, USA, discussed risk-taking behaviour in diabetic youth associated with poor metabolic control, high rate of microalbuminuria and increased risk of DKA. It includes insulin misuse and omission, disordered eating behaviours, inadequate monitoring, falsification of glucose readings, family dysfunction, unprotected sexual behaviour and inconsistent contact with health care team. These behaviours should be conceptualized and addressed by individual and familial counselling, re-education and increasing responsibilities with parental support (11, 12).

Dr Stuart Brink, Boston, MA, USA, showed similar prevalence of substance abuse among diabetic adolescents, as healthy youth. Nicotine causes acute hyperglycaemia, with increased risk for micro- and macrovascular damage. Alcohol may cause acute hyperglycaemia but dangerous late hypoglycaemia. Marijuana intake increases glucose levels and appetite and induces loss of control.

The 'Exercise in T1DM' workshop was conducted by Dr Tim Jones, Perth, Australia, and Dr Steven Green, Dundee, Scotland, whose final recommendations included the need for planning physical activity, glucose monitoring for individual response patterns, considering addition of carbohydrates at an amount of 1–1.5 g/kg/h of activity or decrease in amount of insulin bolus, avoidance of leg sites before activity and reduction of basal insulin overnight (13).

A 'Meal planning' workshop was conducted by Drs Carmel Smart, Newcastle, Australia; Shubnum Haniff-Ismail, Durban, South Africa, and Alan Delamater, Miami, FL, USA. Sole carbohydrate counting and alternative calorie counting are commonly used. 'Stiff' meal planning is not recommended because it is not followed by families. Some 'not to do' behaviours were presented; these included patronizing, scaring and expertize challenging. It was suggested that by using the Motivational Interviewing Model, a more effective behavioural change can be attained because it is client centred, builds rapport and allows the patient to set treatment goals and agenda (www.motivationalinterview.org).

A parenting skills workshop was conducted by Dr Tim Wysocki, Jacksonville, FL, USA. The role

and influence of caregivers are limited by the importance of autonomy, although better outcome was shown in families who maintained parental involvement and who had better diabetes knowledge (12). A few suggestions were discussed: positive reinforcement is better than criticism; express concern and not anger or frustration; building up self-esteem should be present daily; blood glucose fluctuation should evoke discussions rather than arguments; problems should be solved with rather than for the adolescents and decrease involvement incrementally, as an act of motivation and not as a reaction to burnout. The team should review parents' and child's responsibilities annually; questions should be directed to the adolescent and should be solved with him; techniques such as family therapy, teamwork intervention, coping skills training and motivational interviewing should be considered (12) (www.motivationalinterview.org).

The Prevention and Cure symposium featured Dr Desmond Schatz, FL, USA, who presented an overview of the novel cellular therapies for the prevention and amelioration of T1DM and suggested possible future success by a combined 'cocktail' of therapeutic approach of immunomodulation considering autoimmunity control, beta-cell regeneration and protection or replacement of beta-cell mass. The immunoregulatory cell therapies include autologous cord blood, dendritic cells, mesenchymal stem cells and 'non-myeloablative' haematopoietic stem cells, aimed at stimulation of pancreatic regeneration, transdifferentiation into insulin-producing cells and restoration of immune tolerance through regulatory T-cell function. A few initial encouraging results were presented (14–18). Dr C. Wasserfall, from the same centre, presented data showing that 86% of non-obese diabetic mice treated with a combination of anti-thymocyte globulin and granulocyte-colony stimulating factor (G-CSF) showed diabetes reversal with less insulitis, greater insulin preservation and higher CD4/CD8 tolerance index.

Dr Terence Wilkin, Plymouth, UK, the founder of the accelerator hypothesis, showed that beta-cell loss may be accelerated by obesity, with different behaviour of beta-cell mass in those who are most insulin resistant compared with the most sensitive. In a large cohort of healthy children (EarlyBird study), those who are least insulin sensitive have a significant tendency of blood glucose elevation and decrease in beta-cell reserve around the age of 8 yr, with only a short-lived insufficient compensatory rise in insulin sensitivity, while the most insulin-sensitive children do not show that pattern. Family studies of body mass index showed gender-assorted weight gain, which implies that childhood obesity is not of itself a disorder but a result of exposure to an overweight role model (19–21).

Dr Dorothy Becker, Pittsburgh, PA, USA, recipient of the ISPAD Lifetime Achievement Award for 2008, presented the environmental approach to T1DM. An environmental factor or multiple factors are required to cause the autoimmunity, resulting in T-cell collection around the edges of an islet cell, leading to peri-insulitis and later insulitis with positive humoral markers. Candidates for autoimmunity are enteroviruses, mycotoxins, cow milk, cereal content, lack of omega-3 fatty acids, vitamin D insufficiency and abnormalities of the gut mucosal barrier enabling early exposure of the gut lymphoid tissue (22–26).

The joint European Society for Paediatric Endocrinology (ESPE) and ISPAD symposium was dedicated to the renin angiotensin system (RAS) in diabetic nephropathy (DN). Dr Etienne Sochett, Toronto, Canada, showed the association between hyperglycaemia, RAS function, proteinuria and renal damage. The early stages of DN are attributed to initial glomerular hyperfiltration with increment in kidney size, manifested as increased urinary albumin secretion, leading to the late stages with structural changes, mesangial proliferation and end-stage damage. Hyperglycaemia contributes to the activation of intrarenal RAS. Blockage of the RAS improves decline in renal function but does not change outcome (27).

Dr Robert Gardiner, Montreal, Canada, presented the results of the RAS Study, a primary prevention trial of DN using enalapril, losartan or placebo, performed in adults. Renal biopsy was performed at initiation, after 5 yr of treatment and after 6 more weeks of washout period, showing no differences in blood pressure, kidney structure and Glomerular filtration rate (GFR). However, the progression of retinopathy was significantly reduced among those receiving losartan (28).

Dr David Dunger, Cambridge, UK, discussed the rationale of cardiorenal protection studies in adolescents. There is a proportional association between diabetes duration and general endotheliopathy. The cumulative probability of developing microalbuminuria as a marker of the endotheliopathy is related to age at onset, gender, puberty and glycated haemoglobin (29). Morning albumin creatinine ratio was associated with lack of nocturnal decrement of diastolic blood pressure, renal size, increased GFR and dyslipidaemia (30). He described the currently recruiting primary prevention study of dyslipidaemia and nephropathy during pubertal years receiving combinations of statin and angiotensin converting enzyme (ACE) inhibitor or placebo.

Complications, genetics and immunology session

Dr A. Lin, Melbourne, Australia, received the 'Best Oral Presentation Award' for demonstrating quantitative structural differences in the thalamus and lentiform nuclei of young adults with T1DM, possibly related to the finding of the accelerated brain ageing hypothesis. The same group demonstrated differences in

neuropsychological profiles of young diabetics after 12–15 yr of disease; those with earlier disease onset performed poorer (31).

Dr Franco Chiarelli, Chieti, Italy, demonstrated increased kidney volume and renal resistive indexes in diabetic normoalbuminuric youth. Negative association was found between those parameters and plasma levels of endogenous secretory receptor for advanced glycation end products (esRAGE).

Dr H. Siljander, Helsinki, Finland, demonstrated that a low first-phase insulin response, higher insulin autoantibodies and higher insulin resistance are parameters associated with increased progression rate to T1DM among children with human leukocyte antigen (HLA) susceptibility and multiple autoantibodies. Dr Olga Kordonouri, Hannover, Germany, demonstrated that the presence of islet antigen-2 antibody is positively associated with DR4-DQ8 and inversely associated with DR3-DQ2 HLA types but not with PTPN22 polymorphism.

Dr Marian Rewers, Denver, CO, USA, presented data from the Diabetes AutoImmunity Study in the Young (DAISY). The risk of T1DM by 12 yr was 24% in first-degree relatives with HLA DR3/4, DQ8 haplotypes, 4% among all other first-degree relatives and 1% in the general population with DR3/4, DQ8. Positivity to Zn78 autoantibodies was evaluated.

The Loop Club symposium

Dr Lynda Fisher, Los Angeles, CA, USA, summarized the news about continuous glucose monitoring systems (CGMS) as 'We can see what we have not seen before'. Five CGMS are available but are not approved to substitute finger stick measurements. The systems differ in wearing time, alarms and trends display. Their use may introduce possible HbA1c reduction (32, 33) using suggested treatment algorithms (34). Dr William Clark, Charlottesville, VA, USA, discussed the possibility of monitoring glucose levels and predicting hypoglycaemic events with the help of CGMS by presenting the rate and direction of glucose level change. Dr Ragnar Hanas, Uddevalla, Sweden, outlined teaching strategies for starting Continuous Subcutaneous Insulin Infusion (CSII), indicating that although the indications for initiating CSII are similar worldwide (high HbA1c, recurrent severe hypoglycaemia, unstable blood glucose, irregular eating habits, pain from needles and QoL), the therapy regimens are different.

Obesity and type 2 diabetes mellitus symposium and session

Dr Dankwart Wittenberg, Pretoria, South Africa, discussed the role of infant nutrition, showing that breastfed babies grow more slowly but with a reduced risk of overweight when prolonged (35). High early protein intake has long-term consequences as an unfavourable body composition and risk for obesity in later life (36), and early postnatal diet can lead to altered gene methylation and express enhanced epigenetic lability to early nutritional influences (37). Dr Claire Levy-Marchal, Paris, France, outlined that young adults born small for gestational age are at higher risk to develop insulin resistance and metabolic syndrome because of increased catch-up growth. Several hypotheses have been proposed pointing to the role of a detrimental foetal environment, a genetic susceptibility or an interaction between the two and of the particular dynamic changes in adiposity that occur during catch-up growth (38). It still remains unclear how it is linked to insulin resistance. Dr Claudio Maffeis, Verona, Italy, stated that the main target in obesity management should be a whole family setting change in behaviour to a negative energy balance (39). Data of various diets, medications and bariatric surgery are lacking in children and not in consensus. Dr Warren Lee, Singapore, reviewed the phenotype of type 2 diabetes in young children: obese, often pubertal with positive history of diabetes in family. Diagnosis is by an oral glucose tolerance test, urine screening and fasting glucose measurements. The treatment should focus on glycaemic control with metformin and insulin and on controlling hypertension, fatty liver, hyperlipidaemia and obesity (40).

Dr H. Boerschmann, Munich, Germany, demonstrated that the development of overweight in early childhood is influenced by large birth weight, insulin treatment during pregnancy and earlier onset of maternal obesity.

Dr L. Voss, Plymouth, UK, showed data from the EarlyBird Study, that youngsters from all urban neighbourhoods affected by an increasingly obesogenic environment may be vulnerable to obesity, metabolic disturbance and risk for diabetes.

Dr O. Rubio-Cabezas, London, UK, demonstrated that pancreatic developmental disorders are responsible for 7.5% of permanent neonatal diabetes. Fifty-five percent have isolated pancreatic agenesis, which seems to be a recessive condition, while 45% show extrapancreatic features, most cases spontaneous. In the majority, the genetic defect is unknown.

Dr Mark Sperling, Pittsburgh, PA, USA, presented evidence and raised ethical issues regarding four of the current controversies in paediatric diabetes: whether T1DM and type 2 diabetes mellitus are distinct entities or the extremes of the same situation, can DKA-related cerebral oedema be prevented using fluids, electrolytes and insulin judiciously only, are CSII and multiple daily injections (MDI) similar or one superior in achieving better control and QoL and should youth participate in the novel cellular therapeutic trials.

The ISPAD debate was dedicated to hypoglycaemia

Dr Joseph Wolfsdorf, Boston, MA, USA stated that the risk of severe hypoglycaemia is the goal limiting factor in diabetes care and significantly higher among youth than adults. Defective glucose counterregulation causes hypoglycaemia-associated autonomic failure, recurrent hypoglycaemia episodes and unawareness, leading to anxiety, reduced insulin dose and acceptance of higher glucose levels. The ways to manage that fear is to address it frequently, to educate strategies for prevention, to do frequent glucose checks, use insulin analogues, individualize glycaemic targets, and remember that children with lower HbA1c are not at higher risk for severe hypoglycaemic events (41). Liz Northam, Parkville, Australia, stated that diabetes alters the function of the central nervous system (CNS) in the developing brain by both hypoglycaemia and hyperglycaemia (42, 43). Chris Ryan, Pittsburgh, PA, USA, defended the 'diathesis hypothesis' that hyperglycaemia is particularly harmful to the CNS in early life and leads chronically to microvascular diseases and consequently to cerebral hypoperfusion in later life. He presented data supporting the claim that severe hypoglycaemic events are not as harmful as thought (44, 45).

Dr Francois Bonnici, Cape Town, South Africa, the awardee of the most distinguished Lestradet ISPAD Prize, for an outstanding contribution in the field of diabetes education, highlighted the need for education and advocacy, the dominance of numeracy and emotional intelligence and told the audience that 'Going beyond the numbers is part of good diabetes care' and that one should remember that 'It is with the heart that one sees right, what is essential is invisible to the eye.' 'The Little Prince'.

Dr Wojciech Młynarski, Łódź, Poland, received the Young Investigator Award. His work is an example of the contribution of one case from clinical practice to basic science and to medical treatment breakthrough. A case of a girl with a novel KCNJ 11 mutation, His46Leu, causing intermediate DEND syndrome (Developmental delay, Epilepsy, Neonatal Diabetes) (iDEND), responded to glibenclamide therapy by improving glycaemic control, motor functioning and even blood flow and function of the CNS (46).

Dr A. Ponsonby, Parkville, Australia, received the Best Poster Award for describing the associations between allelic variants of the vitamin D receptor gene and T1DM onset and their variation according to ambient winter ultraviolet radiation levels by a meta-regression.

The 34th annual meeting was a resounding success, and congratulations are in order for the local organizing committee of Drs Kuben Pillay (Chair), Areti Philotheou, David Segal, Kiran Parbhoo and Steve Delport. We all look forward to ISPAD 2009 in Ljubljana, Slovenia.

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