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Review Article

The paradigm of pediatric diabetes – art vs. science. Meeting Highlights – 31st Annual ISPAD Meeting, August 31 – September 3, 2005, Krakow, Poland

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International Society for Pediatric and Adolescent Diabetes (ISPAD) meetings have traditionally been comprised of a mixture of quantitative scientific research, qualitative research, opinion, and consensus. At its best, this combination creates a milieu where science informs clinical practice, yet at its worst, it might produce a 'polyglot' of non-consensual 'agreement' and selective science that is used to justify opinion which results in confusion, discord, and inconsistent clinical practice. Clearly, the struggle to achieve the former outcome is the priority for ISPAD and based on the content of this year's meeting program, there is good evidence that a further step has been made in the right direction.

One of the main highlights of ISPAD 2005 was the excellent symposium discussing the 'new' hypotheses about the etiology of type 1 diabetes mellitus (T1DM). Professor Mikael Knip (Helsinki, Finland, Abstract not submitted) discussed evidence supporting the 'Hygiene Hypothesis' using the geographic juxtaposition of Finland and the adjacent Karelia territory of the Russian Federation as a natural laboratory to inform on this debate. While the Finns share a common human leukocyte antigen (HLA) genotype (DQ subtype) with the population in Karelia, the incidence rates of T1DM between 1990 and 1999 showed a sixfold difference between the two areas. Cross-sectional data reveal serological evidence of markedly different exposure rates to various infectious agents (e.g., *Helicobacter pylori; Toxoplasma gondii; coxsackie A*, and *hepatitis A*). While total immunoglobulin E (IgE) levels were greater in the Karelian population, the allergy-specific IgE levels were three to fourfold less. Counterintuitively, Karelian school children showed higher rates of positivity to islet cell antibodies (ICAs), insulin autoantibodies (IAAs), and glutamic acid decarboxylase antibodies but lower rates of IA2. A critical review of the immunologic Th1/Th2 paradigm and the experience of other populations such as Japan suggest, however, that exposure to infectious agents *per*

The citations appearing after the various authors' names correspond to the Abstracts for the 31st Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD), August 31 –September 3, 2005, Krakow, Poland. Issue, PEDIATRIC DIABETES, Volume 6, Supplement 3, September 2005. Legend: L, Lecture; O, Oral Presentation; P, Poster Presentation.

se is not an adequate explanation for the variation in incidence of T1DM. Rather, it was proposed that the role of indigenous microflora and host microbe infections might be pivotal to this phenomenon.

Professor Terry Wilkin (Plymouth, UK, L. 3, p. 2) proposed an alternate etiologic basis for T1DM in a cogent, but nonetheless, polemic presentation that put forward the case for the so-called 'Accelerator Hypothesis'. In this model, T1DM and T2DM are viewed as the same disorder of insulin resistance set against differing genetic backgrounds and can be considered a disorder of β-cell function with three variables (or 'accelerators') determining disordered glycemia, with or without the requirement for insulin therapy. The first accelerator is the constitutional background of an individual expressed as an inherent susceptibility to β-cell apoptosis. The second unifying accelerator is insulin resistance – stressing the β cell and increasing its antigenicity. The third deficiency is the immune responsiveness of the individual, defined in part by HLA subtype. The predictions of the Accelerator Hypothesis are that (i) the incidence of T1DM should increase with increasing rates of obesity/insulin resistance; (ii) newly diagnosed patients with T1DM should be heavier at disease onset; (iii) heavier children should have earlier disease onset; (iv) as the incidence of T1DM increases with obesity, fewer cases should be because of genetic susceptibility, and more cases should result from increased insulin resistance; and (v) as genetic susceptibility gives way to environmental risk, T1DM will become indistinguishable from type 2 disease. Epidemiological data (auxological and serological) from several European, North American, and Australian studies were provided in support of these hypotheses; however, in the lively debate following this lecture, it was highlighted that data providing direct evidence of increasing insulin resistance prior to the onset of T1DM are lacking. The concept that the Accelerator Hypothesis describes an 'autoimmune response to an industrialized environment' is clearly controversial and will continue to be debated.

Professor Andrew Hattersley (Exeter, UK, L. 1, p. 1) presented an excellent keynote lecture on the monogenic causes of diabetes in childhood and adolescence, emphasizing the utility of molecular genetic testing in suspected cases of non-T1DM and T2DM in this age group. The importance of establishing an early diagnosis in these relatively rare cases of diabetes was discussed, arguing that it would allow for more appropriate diabetes treatment, optimization of glycemic control, and prediction of future prognosis to be achieved earlier. This point was highlighted through the presentation of a number of clinical cases, including that of an infant presenting with neonatal diabetes secondary to a mutation in the *KIR6.2* gene. The striking genotype–phenotype relationships observed in this condition, ranging from a transient neonatal diabetes form to a more severe form of permanent neonatal diabetes associated with developmental delay and epilepsy (DEND syndrome), were presented. KIR6.2 mutations are associated with reduced K_{ATP} channel closure in a number of different tissues including the pancreas, muscle, nerve, and brain. Those mutations resulting in the most severe K_{ATP} channel dysfunction seem to be associated with neurological problems. Data were presented which demonstrate that, in some instances, the diabetes associated with the KIR6.2 mutations can be improved with treatment with the use of sulfonlyurea agents, which can restore closed K_{ATP} channel function via non-ATP-dependent mechanisms. Unfortunately, sulfonlyurea treatment seems to have no impact on the neurological problems seen in the DEND syndrome, although, intriguingly, a less severe, intermediate form of DEND may be amenable to this type of treatment. The reasons for these differential effects remain to be elucidated.

The ever increasing complexity of the role of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis in the pathophysiology of T1DM and in the development of microvascular complications was explored in a symposium introduced by Professor David Dunger (Cambridge, UK, L. 5, p. 3). Data were presented by Ake Sjoholm (Stockholm, Sweden, L. 6, p. 3), outlining the emerging body of evidence, suggesting that IGF-I plays a critical role in the control of β-cell survival and in the regulation of cell death through inhibition of cytokine-induced activation of apoptotic pathways. In animal experimental models, IGF-I administration protects against streptozocin-induced β-cell destruction, delaying the process leading to eventual hyperglycemia and diabetes, whereas, in contrast, IGF binding protein (BP)-3 has been shown to increase β-cell apoptosis through increased DNA fragility. These observations raise the intriguing possibility that manipulation of the GH/IGF-I system may provide some possible therapeutic advantage in delaying the progression and onset of T1DM. New insights into the pathogenesis of diabetic nephropathy were presented by Professor Alan Flyjberg (University of Arhus, Denmark, Abstract not submitted), who highlighted the complex interrelationships that exist between various hemodynamic, metabolic, intracellular and growth factors in the development and progression of diabetic kidney disease. Data in support of the 'GH hypothesis', whereby the effects of GH hypersecretion and the resulting increased paracrine production of IGF-I within the tissues are thought to be involved in the etiology of diabetes-related microvascular disease, were presented. This included data from novel animal models such as the total GH receptor knockout mouse (Laron mouse), which seems to be protected from developing diabetic kidney disease following the induction of diabetes. Administration of a specific GH receptor antagonist (Pegvisomant) normalizes kidney growth

and prevents against diabetic kidney disease in animal models of diabetes, particularly when given in combination with angiotensin converting enzyme inhibitors. Thus, manipulation of the GH/IGF-I axis with pharmacological agents offers the opportunity to prevent or slow the progression of diabetic kidney disease, and clinical trials in humans are now underway.

The theme of the GH/IGF-I axis and the use of new drug treatments were further explored in a symposium dedicated to the topic of adjunctive therapies and their role in the management of type 1 diabetes. Disequilibrium in the GH/IGF-I axis is thought to play a pivotal role in the increased insulin resistance seen in type 1 diabetes, particularly during puberty and the adolescent years. Intensification of insulin therapy is limited by problems with hypoglycemia and excessive weight-gain, and there seems to be a sound physiological rationale for the use of insulin-sensitizing agents in addition to insulin therapy during these difficult years. Clinical trial data on the use of subcutaneous recombinant human IGF-I (Carlo Acerini, Cambridge, UK, L. 14, p. 7) and on the use of oral insulin-sensitizing agents such as Metformin (Jill Hamilton, Toronto, Canada, Abstract not submitted) were presented, which suggest that these adjunctive therapies may have a place in the treatment of T1DM, although further clinical studies are required to confirm their long-term safety and efficacy.

The Loop Club Symposium this year focused on real-time continuous glucose monitoring, and interesting data from the multicentre Guard Control Trial were presented. In this randomized controlled trial of 162 adult and pediatric patients with diabetes using the MiniMed Guardian Continuous Glucose Monitoring System (CGMS) device, 3-month follow-up data revealed a mean improvement in the HbA1c of 0.8% and fewer hypo- and hyperglycemic excursions in the pediatric subgroup using the device. Although patients were not given response algorithms to the blood glucose data that they were obtaining from the device, 98% of the participants were making changes to their insulin dose, carbohydrate intake, or their lifestyles in response to the information. Technical data pertaining to the Abbott Freestyle Navigator were also presented, a system that seems to have a number of attractive features, including a reported greater accuracy of measurement at lower blood glucose values. In addition to this, mean absolute relative difference in blood glucose levels have been found to decrease with time, thus making the sensor apparently more accurate and requiring less calibration towards the end of its 5-day lifespan. However, it is apparent that both CGMS systems continue to struggle with accuracy in dynamic glucose conditions with a 'lag' of 5–8 min between measured interstitial glucose and true blood glucose values.

The final symposium on the program on the birth and death of the β-cell, presentations by Drs Otonkoski (Helsinki, Finland, L. 17, p. 8) and Eizirik (Brussels, Belgium, L. 18, p. 8), provided a comprehensive review of what is currently known of the cellular-signaling processes defining β-cell ontogeny and death/apoptosis. Particular attention was paid to the role of the epidermal growth factor receptor in defining β-cell mass and proliferation in the mouse model. The importance of interaction between the pro-apoptotic cytokines interleukin-1β and interferon-γ and the transcription factor NF-κβ was also emphasized. Ongoing research in this field has been greatly enhanced by the development of a Beta Cell Gene Expression Bank that can be accessed online at: http://t1dbase.org/cgi-bin/enter_bcgb.cgi

In addition to the symposia described, this year's ISPAD meeting was also notable for the number and quality of short oral presentations and posters. Significant research findings as to the etiopathogenesis of T1DM included data from the Diabetes Prediction and Prevention Project study from Finland (Sijander et al. O. 2, p. 10). In individuals with an increased HLA-associated risk, a combination of sequential screening with ICAs and IAAs was found to have a positive predictive value of 47.8% over 5 yrs. Data from the German-Austrian Cystic Fibrosis-related Diabetes study group reviewed data from an annual screening program with the oral glucose tolerance test from 10 yrs of age (Holl et al. O. 3, p. 10). In this study, 7.9% of patients were found to have diabetes by 18 yrs of age with an increased incidence in females (12.5 vs. 4%). Two-year data from the largest pediatric insulin pump study (The PedPump Survey) were also presented (Jarosz-Chobot et al. O. 15, p. 14). In this international survey of 1086 pump patients from 30 centers, early data indicate that one of the keys to improved metabolic control is the frequency of insulin boluses given per day (>7 appears beneficial) and not over-reliance on basal insulin infusion rates. However, not all children and adolescents respond well to 'intensified' therapy. A report from Wigan in the United Kingdom (Robinson et al. P. 58, p. 48) showed that a switch from twice daily to basal-bolus insulin injections resulted in a significant deterioration in metabolic control, indicating that the wholesale adoption of intensive therapy may be counterproductive in some instances. Intriguing data were presented from the Hvidore Study Group showing that observed differences in diabetes outcomes between various international centers were largely attributable to 'disease-severity' at diagnosis rather than center characteristics (Mortensen et al. O. 14, p. 14). In addition to this, diabetes disease severity (measured in part by baseline HbA1C) was predictive of metabolic control 4 yrs later, implying that individuals at risk of future poor metabolic control may be able to be identified

from the point of diagnosis. Finally, data from Canada showed a disturbing number of children (48.7%) presenting with diabetic ketoacidosis (DKA) at diagnosis may have been misdiagnosed in the week prior to presentation. This finding has obvious implications for primary care where efforts need to be directed if the incidence rate of DKA in newly diagnosed patients and the potential catastrophic complications arising from it are to be reduced.

Overall, the 31st Annual Meeting of ISPAD can be considered a success, demonstrating that the Society has matured into a forum committed to communicating quality laboratory and clinical research relevant to the field of pediatric diabetes. The fusion of art and science in clinical practice has the potential to greatly enhance the diabetes care experience. However, the practice of evidence-based medicine demands that these two components of care be used in a complementary, rather than, interchangeable manner. Rigorous science must be used to inform the art of clinical practice. ISPAD meetings will, and should, continue to overtly distinguish between these two paradigms, ensuring the benefits of each, yet avoiding the confusion of indiscriminate admixture.