

Review Article

Report of the 35th ISPAD-Meeting, Ljubljana, Slovenia, 2-5 September 2009

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Introduction

The 35th annual meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD), held in Ljubljana, Slovenia, was entitled ‘Translation Research in Pediatric Diabetes’ and aimed to discuss ways to bring findings from basic and clinical research into the management of children and adolescents living with diabetes.

Weds, Sept 2nd: Opening Session–Metabolomics

Dr. Orešič, Finland, gave an overview about his research on metabolomics in children with type 1 diabetes (T1DM). He reported on individuals who were investigated prospectively in the Diabetes Prediction and Prevention Study (DIPP) and who later developed diabetes. These individuals already had reduced levels of succinic acid and phoyphatidylcholine in infancy; later on, they demonstrated reduced levels of triglycerides and antioxidant ether phospholipids

as well as increased levels of proinflammatory lysophosphatidylcholines several months prior to seroconversion to autoantibody positivity. He and his group then investigated NOD-mice and observed similar changes, prior to the development of T1DM(1).

These novel findings on pre-autoimmune alterations may lead to a clearer understanding of the pathogenesis of T1DM.

Plenary Session I: Translational Research in Pediatric Diabetology

Prof. Franco Chiarelli, Italy, spoke on the concept of systems biology in pediatric diabetes. He was followed by Prof. Moshe Phillip, Israel, who presented data about using the MD-logic to close the loop and create an artificial pancreas. The last speaker, Prof. Nataša Bratina from Slovenia addressed continuous glucose monitoring (CGM) and the translation of research trials using these technologies into clinical practice.

Plenary Session II: New Developments in Nutritional Management

Dr. Lori Laffel, USA, presented a comprehensive review of the effect of nutrition on T1DM management. Whereas medical nutrition therapy emphasizes accurate carbohydrate counting and the matching of prandial insulin, the emphasis on CHO may lead to a diet that is not well balanced with regards to protein, fat, and other nutrients as demonstrated by the results of the SEARCH for diabetes in youth study (2). Also, she highlighted data that demonstrate that adherence to dietary management is associated with improved glycemic control. Interestingly, research suggests that *consistency* may be more important than *accuracy* in carbohydrate counting for achieving improved glycemic control (3).

Prof. Paolo Pozzilli, Italy, reviewed nutrition for competitive athletes with T1DM. He highlighted the important and complicated relationship between the type of exercise (anaerobic versus aerobic), the intensity and the duration of exercise, and counter-regulatory hormone secretion. Frequent or continuous glucose monitoring, and careful nutritional planning, are vital to the success of an athlete with T1DM. Dr. Olga Kordonouri, Germany, discussed the use of dual-wave insulin boluses to cover meals that are high in carbohydrate, protein, and fat. She reviewed a recent publication from Pańkowska et al (4) that demonstrated improved glycemic control when using an algorithm that took into account not only carbohydrate, but also protein, and fat content. She concluded the lecture with her own group's experience with a prospective, randomized clinical trial comparing different bolus algorithms (dual-wave vs. standard, carb based vs. carb-protein- fat based).

Oral Sessions I Diabetes

Acute and Chronic Complications:

Dr. Fritsch, Austria, reported data from a large German-Austrian cohort (>28.000 patients), investigating the frequency of recurrent DKA in patients with T1DM. A large majority of the patients had no episodes of DKA, whereas the rate of DKA was significantly higher in females, in immigrant children and in the early teenage years. Dr. Cho, Australia, presented data on complication screening after 2-5 years of diabetes over a period of 17 years. Briefly, HbA1c and retinopathy decreased over the time period whereas the rates for microalbuminuria, albumin excretion and peripheral nerve abnormality did not change significantly.

Dr. Perantie, USA, discussed the longitudinal change in brain volume with glycemic extremes in youth with T1DM using MRI-imaging. Over a 2-year period, hyperglycemia, but not severe or mild

hypoglycemia, produced measurable effects on gray and white matter.

Dr. Svensson, Denmark, investigated the use of antibiotics in early childhood, comparing children with T1DM with healthy controls using the Danish Prescription registry. No differences between the groups were found; hence they conclude that there is no evidence for an increased incidence of T1DM in children who are subject to treatment with antibiotics.

III Diabetes Care, Education, Psychosocial Issues

Dr. M.F. Housiaux, Belgium, explored the effect of emotional competencies (alexithymia and emotional awareness) on glycemic control. They found that difficulty describing feelings was an important predictor of glycemic control. Dr. N. Patel, UK, described semi-structured face-to-face interviews with 10 parents of school-aged children with T1DM. These parents reported variable amounts of support from the schools with concerns of exclusion and other barriers to optimal glycemic control and significant effect on parents. Dr. A. Serlachius, Australia, found that adolescents wanted to learn more about coping skills and wanted programs that focused on diabetes-related stressors. P.A. Colton, Canada, described a longitudinal study of 75 girls with T1DM showing that family factors, in contrast to individual factors, predicted A1c one year later. M. de Wit, Netherlands, described a web-based survey they used to assess the prevalence of depressive symptoms in youth with T1DM using the Child Depression Inventory. They found that 16.5% of the 230 adolescents had more depressive symptoms, with a higher prevalence in those with higher A1c values. V. Cherubini, Italy, presented data from 14 Italian pediatric centers which reported an improvement in mean A1c across centers since their previous report (8.1% vs. 8.87%). No difference in A1c was found in comparing children treated with MDI to children treated with CSII.

S. Shalitin, Israel, found that younger age, frequent self monitoring of blood glucose, and lower A1c at pump initiation were predictors of good glycemic control on insulin pump therapy. Lastly, D. Elleri, UK, presented results on overnight, closed-loop insulin delivery following afternoon exercise. Nine subjects were studied on two separate occasions following a standardized, afternoon exercise session; once using closed-loop insulin delivery and once using standard insulin pump settings. The closed-loop insulin delivery increased the time the glucose was in target when compared to standard CSII. Still, only one subject had hypoglycemia while on standard CSII and no subjects had hypoglycemia on closed-loop insulin delivery.

Thurs, Sept 3rd

The annual Editorial Meeting of the journal "Pediatric Diabetes" reported that submission of articles to the journal increased from 47 in 2001 to 212 in 2008, with more than 250 submissions anticipated for 2009. The impact factor increased from 2,314 in 2007 to 2,424 in 2008, while time to first and final decision has been significantly reduced.

Plenary Session III

The Young Investigator Award this year went to Dr. Malik, a psychologist working in Amsterdam. He presented an overview of his work (5) explaining the relation between diabetes support and diabetes stress in adolescents.

Pediatric Type 2 Diabetes—Screening, Treatment and National Programs

Dr. Urakami, Japan, reported data from a screening program where the urine of pupils was routinely tested for glucosuria (6). The incidence of type 2 diabetes (T2DM) has increased in Tokyo over the years, >80% of these patients are obese (boys > girls) and 60–70% have a positive family history for T2DM. Birth weight also seems to contribute to risk; they found an association with both low and high birth weight and the development of T2DM.

Dr. Ceriello, UK, stressed the importance of postprandial glucose (PPG) for the development of diabetes complications. Since post prandial hyperglycemia is the most important contributor to HbA1c, targeting this time period is essential to improve metabolic control. The IDF (International Diabetes Federation) guidelines for PPG recognize this and recommend the cut-off for PPG at 140 mg/dl (7, 8 mmol/L) (7, 8).

Dr. Arslanian, USA, focused on T2DM in young patients. She discussed the association between insulin resistance and insulin sensitivity, as well as the difficulties in distinguishing between T2DM and obese T1DM (9). She reviewed the current treatment options/recommendations for T2DM and stressed the important association between obesity, dyslipidemia, hypertension and the risk for cardiovascular events (Metabolic Syndrome) evident in younger age-groups (10).

Symposium II The Loop Club: New Approaches to Artificial Pancreas

There were three presentations during this symposium that focused on new approaches to the ultimate development of the artificial pancreas. Louis Shenkman,

Israel, reviewed continuous glucose monitors currently available including their challenges and limitations. He also reviewed the technology being developed in corneal optical devices as well as recent advances in the P. Cezanne Fluorescence Energy Transfer(FRET)-based continuous glucose monitoring solution, an implanted biosensor that could last 6 months to 1 year. With this system, bacterial glucose-binding protein is hybridized with two fluorescent proteins that exhibit a FRET response to different glucose concentrations. A cell line has been developed that expresses the fluorescent proteins and work is currently proceeding on developing the energy source for the sensor and biocompatibility issues.

A. Caduff, Solianis Monitoring, Switzerland, reviewed the progress to date in the development of a noninvasive Multisensor device for continuous glucose monitoring. He explained the concept of the multisensor; several properties of the skin (temperature, moisture) change with varying glucose concentrations and these perturbations can affect the glucose sensor measurement. The goal of the Multisensor device is to measure these perturbations in the properties of the skin and minimize the effect on the sensor signal, leading to the development of the fully integrated device that is typically attached to the upper arm (11). P. de Vos, Netherlands, reviewed the field of pancreatic islet cell transplantation with a focus on the emerging field of microencapsulation of pancreatic islets. The goal of this technology is to protect the foreign islet cells from the host immune system by surrounding them with an artificial membrane. He discussed current challenges in the field including capsule material and islet produced factors that result in graft failure as well as new approaches to overcome these obstacles .

Symposium III SWEET Dreams: Structure, Process and Outcome Quality in Europe.

The main objective of the SWEET project is to improve the metabolic control of diabetes in children by supporting the development of diabetes centers. Dr. Sumnik reported on the first data from 26/27 EU-countries, who were assessed by questionnaires: although the data are not objective, this database, nevertheless, can form the basis for the development of strategies that may lead towards better and more equal access to modern pediatric diabetes care.

Prof. Danne, Germany, reported on the different collaborations underway with other organizations such as the International Diabetes Federation (IDF) project being funded by the EU together with corporate partners and foundations. The goal is to develop joint recommendations for structure, process and outcome

quality, similar to the already existing Diabetes Data Acquisition System For Prospective Surveillance (Dpv), in which >200 clinics in Austria and Germany are participating. Dr. C. de Beaufort, Belgium, stressed the importance of such reference-centers in setting a standard for each country to improve metabolic control in young diabetes patients in Europe. (www.sweet-project.eu)

Symposium IV Diabetes Interacting with Other Hormonal Axes

During this symposium there were three lectures on other hormonal axes and their effect on diabetes. C. Kanaka-Gantenbein, Greece, discussed thyroid function, stating that approximately 15% to 30% of children and adolescents with T1DM have positive thyroid auto-antibodies and that up to 50% of these children will progress to clinical autoimmune thyroid disease. The speaker emphasized that children with positive thyroid auto-antibodies but without thyroid dysfunction do not require treatment. Given the strong association between autoimmune thyroid disease and T1DM, the common loci/genes for susceptibility for both (CTLA 4, FOXP3) were discussed. The role of androgens and T1DM was given by E. Codner, Chile. She reviewed pubertal delay in males with T1DM and hyperandrogenism in young women with T1DM (12). Peter Bang, Sweden, discussed the complicated relationship between lower circulating levels of IGF1 in individuals with T1DM and the association between IGF1 and diabetes-related complications. This apparent paradox could be explained by the tissue levels of IGF1 and the local IGF1 effects at high glucose levels.

Fri, Sept 4th Plenary Session IV Translational Research in Early Micro- and Macrovascular Complications in Pediatric Diabetes

Kim Donaghue, Australia, provided a thoughtful discussion about risk modeling for diabetes complications. She discussed risk modeling using tissue glycation and presented data that demonstrated that skin collagen and plantar fascia thickness both predict complications (13). Data about the effect that ACE inhibitors and ARBs have on the complications of retinopathy and nephropathy also were reviewed. Risk modeling also takes into consideration those individuals who do not have diabetes-related complications, in an effort to identify possible protective mechanisms.

Lastly, she discussed the risk of complications in relation to insulin resistance, inflammation, and endothelial dysfunction. Alessandro Doria, USA, discussed the different pathways implicated in the development of diabetes-related complications, going from laboratory and eventually into translated clinical research (bench to bedside). Specifically, he reviewed Protein kinase C (PKC) activation, Receptor for Advanced Glycation End products (RAGE activation) and oxidative stress. The point was made that these pathways are implicated in the development of macrovascular complications in individuals with T1DM, and there is strong evidence in vitro and in animal studies. Regrettably, none of these findings have yet been fully translated into available interventions for patients. He concluded with a discussion of the genome wide association approach to identify novel pathways (14). F. Cameron, Australia, reviewed the neuropsychological effect of T1DM in childhood adolescence. The message was that “diabetes is bad for your brain” with the data presented supporting a deleterious effect of hyperglycemia, hypoglycemia and glucose variability on cognition, behavior, and mental health.

Oral Sessions IV Diabetes Genetics, Immunology

J. Ludvigsson, Sweden, presented research that intended to clarify the mechanism of residual insulin secretion preservation in children recently diagnosed with T1DM who received GAD65-alum treatment. They found that individuals who responded to the vaccine had a lower number of activated T cells, an increase in regulatory T cells, and induction of Glutamic acid decarboxylase autoantibodies (GADA). The researchers concluded that these changes may be one explanation of the GAD65-alum effect on residual insulin secretion. R.D. Savoldelli, Brazil presented a case study of identical twin boys with immunodysregulation, polyendocrinopathy enteropathy X-linked syndrome (IPEX) caused by a novel mutation in FOXP3 with discordant phenotypes. P. Kotnik, Slovenia, presented work that compared the PTPN22 genotype and frequency of c1858t polymorphism in 75 subjects with T1DM and Hashimoto's thyroiditis to subjects with T1DM alone. The c1858t polymorphism in PTPN22 gene was not associated with the joint susceptibility for T1DM and Hashimoto's thyroiditis. Of two presentations from the same group in Brisbane, Australia, the first investigated the timing of IL-1 secretion, the source of IL-1 secretion, and possible drivers of IL-1 secretion in NOD mice. The investigators found that NOD mice splenocytes secrete IL-1 between 6–16 weeks at the onset of insulinitis, prior to diabetes. IL-1 was also produced by monocytes and dendritic cells in the islet. They found that IL-1

over-production is driven by autoantigen presentation. The second study investigated NF-kappa B signaling in siblings at risk of T1DM. NF-kappa B is a transcription factor family involved in RelB transcriptional activity which controls dendritic cell and thymic function. They found that RelB nuclear activity was 2-5 fold higher in subjects with T1DM, possibly activated by environmental factors. Dr. C. Chiavaroli, Italy, presented data on insulin resistance and oxidative stress in obese and non-obese pre-pubertal children born either small or large for gestational age. They found increased insulin resistance and oxidative stress in prepubertal normal-weight small for gestational age (SGA) and large for gestational age (LGA) children with an additional impact of obesity, suggesting that birth weight and obesity are independent risk factors.

VI Diabetes Project in Developing Countries

Diabetes in developing countries was discussed in a symposium, as well as an oral session. In these countries no one can identify the correct numbers of children with diabetes or their outcome. Most of the developing countries also suffer from different communicable diseases. This double burden leads to an even bigger financial and organizational problem, with only few pediatricians who are trained in pediatric diabetes. Some countries are still having problems supplying insulin and syringes to their patients, let alone BG-strips, which are mostly unaffordable to the families. A study from rural India, reported an equal female: male ratio (100:100) of diabetes in the age group <15 yrs, but a female: male ratio of 57:100, in adults implying that roughly half of the girls are lost to follow up. Fortunately these numbers are different in metropolitan areas, where the ratio remains equal.

Symposium V

A Heavy Problem: Treating Overweight in Adolescents with Type 1 Diabetes

The symposium was chaired by Dr. Ragnar Hanas, Sweden and Dr. Andreja Čampa, Slovenia. Three speakers addressed the growing problem of overweight and obesity in adolescents. This topic has emerged as a major issue for children with diabetes throughout the world. Dr. Olga Ramos, Argentina, spoke about the prevalence of obesity in youth with T1DM followed by Dr. Alicia Jenkins, Australia, who addressed lipids modifying cardiovascular risks in overweight T1DM. The last speaker, Dr. Andrej Janež from Slovenia, offered insights into the treatment of obesity in T1DM.

Symposium VI: summer camps

This Symposium gave an overview about diabetes camps in different European countries, namely France, Slovenia, Poland and Austria.

All speakers emphasized the importance of diabetes camps for building self-esteem, encouraging self-management by children with diabetes and contributing to the long-term goal of improving metabolic control, issues that were stressed by Maslow et al in their recent review (15).

Sat, Sept 5th

Plenary Session V: Lestradet Award Lecture

This years Lestradet Award was given to Dr. Viorel Serban from Romania. For more than 20 years, Dr. Serban has been instrumental in the improvement of care for children with diabetes in Romania by initiating a diabetes center for children and organizing annual meetings for the training of pediatricians. (16).

Translational research in Psychology: Changing Behavior in the “Difficult” Adolescent

The last plenary session of the meeting addressed different aspects of psychology. Dr. Gregory from the UK gave an overview of the psycho-educational tools targeting poor adherence in adolescents. Motivational interviewing is one approach which has shown promising initial results. It appears to help decrease HbA1c, lessen anxiety, and increase the sense of well being and life satisfaction. He then explained the DEPICTED program, which has developed a training package for health care professionals to aid them in promoting a counseling style specifically designed to help adolescents with diabetes to modify their self-management in an effort to improve metabolic results (17).

Dr. Radobuljac from Ljubljana then gave a talk about risky behavior in adolescents including suicide and other self injurious behavior. Her group found that T1DM was rather protective for most of these risky behaviors, finding higher numbers in controls (assessed by a questionnaire). In contrast females with T1DM are at higher risk of developing an eating disorder (18).

Finally Prof. Daneman, Canada, talked about inter- and intrapersonal barriers to achieving the goals of metabolic control. Interpersonal factors are e.g. family factors (e.g. low cohesion, poor organization), parental factors such as fear of hypoglycemia or mental illness) and other (e.g. socioeconomic factors). Intrapersonal factors are e.g. anxiety, learning disabilities depression or eating disorders. He gave an overview of the existing literature and stressed the importance of determining

the specific barriers in the individual family to be addressed. In addition, it is necessary to refer to qualified mental health care professionals.

Symposium VIII: ISPAD/EURODIAB Symposium on Childhood Diabetes

This symposium focused on the epidemiology of childhood diabetes. Gisela Dahlquist reported nationwide data from Sweden covering the age group 0–34 years, where there has been a shift into the younger age group, the incidence increased only in the age group 0–14 yrs.

The Hungarian Childhood Diabetes Epidemiology Study Group has investigated the duration of symptoms before diagnosis, the clinical presentation and the frequency of DKA over a 7 yr time period. The rate of onset-DKA was around 30% (highest in the youngest age group), the mean duration of symptoms prior to diagnosis was 14 weeks, less in the younger age group, who were also more likely to present in metabolic decompensation.

Last Dr. Cardwell from Belfast gave an overview about his analysis of perinatal risk factors in the literature. In short: Children, who are born heavier and by Cesarean section, have consistent increases in T1DM risk.

Symposium IX Food Fight: Diabetes and Eating Disorders

The last symposium of the conference was a review of the epidemiology, diagnosis, and treatment of eating disorders in individuals with T1DM. Barbara Anderson, USA, reviewed the prevalence of disordered eating in individuals with T1DM (19). Young women with diabetes have 2.4 times the risk of developing an eating disorder and nearly 30% of diabetic women of all ages admit to using insulin to restrict weight. Dr. Anderson reviewed the warning signs of disordered eating to which diabetes clinician should pay attention. She also reviewed key questions that should be asked of a patient when screening for disordered eating. Karin Lange, Germany, reviewed their education program developed in part to prevent and treat eating disorders in youth with diabetes. They have developed four interactive modules for small groups as part of a diabetes education program for adolescents. The last speaker, P. Colton, Canada, focused on the psychological themes often present in individuals with T1DM and eating disorders: control, mood regulation, rebellion or protest, and escape. She also discussed an approach to the management of eating disorders in diabetes clinic including the importance of setting a deadline for referral, making stepwise small changes,

having the patient and clinician write out goals, and the patient keeping a diary of blood glucose data, emotions, food, insulin omission.

Poster Session

There were lively poster sessions with excellent research presented by young and established researchers.

Summary

During the 35th annual meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD) friends and colleagues new and old from around the world had an opportunity to convene in beautiful Ljubljana, Slovenia to discuss the ways in which we are improving and could continue to improve the lives of youth with diabetes. The five day meeting was filled with exciting plenary sessions, symposia, oral presentations as well as abstract and poster sessions. The principal focus of the meeting was on the translation of basic research findings into clinical research and the translation of clinical research into clinical practice.

There are multiple examples from among the meeting highlights that illustrate the concept and importance of translational research. One fine example was the opening session on metabolomics; if we could understand the pathogenesis of T1DM starting even before the development of autoimmunity, then we would have opportunities for future clinical research and eventual interventions to prevent T1DM. The lecture given by Alessandro Doria, United States, entitled Complications-causing Pathways in Macrovascular Disease, was also an excellent example of how lessons learned from basic science research were translated into animal studies and eventually into clinical research. The Loop Club session discussed how advances made in the field of continuous glucose monitoring are just now being translated into clinical research with human subjects. Lastly, invited lecturers reviewed important, recently published literature that may affect clinical practice. Some examples include using novel algorithms for dual-wave boluses in insulin pump therapy, specifically targeting post-prandial hyperglycemia in youth with type 2 diabetes, novel approaches to the teenager with T1DM and poor adherence, and screening strategies for eating disorders in patients with diabetes.

There were several sessions, oral abstracts and posters dedicated to diabetes in the developing world. It was amazing to hear how these clinicians and scientists have translated the strategies and experience from developed countries into programs for children with diabetes in the developing world.

The 35th annual meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD)

concluded with the closing ceremony and transfer of the ISPAD flag to the host of our next meeting in October, 2010 in Buenos Aires, Argentina.

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