ISPAD2010

INVITED SPEAKERS

Absence of Chronic Complications in Youth – Vision or Reality?

INV01

Epigenetic changes associated with the legacy of hyperglycemic memory

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Objectives: Diabetes and its consequence of accelerated vascular complications is a major global clinical problem. Of particular interest is the phenomenon of metabolic memory whereby diabetic patients, despite improved glycemic control, develop complications as a result of prior poor glycemic control. It still remains unknown as to the molecular mechanism conferring hyperglycemic memory and how this specifically leads to a program of diabetic vascular complications. We have postulated that epigenetic modifications are associated with key inflammatory pathways, more specifically, we hypothesize that histone code changes, participate in this phenomenon.
Methods: Human primary endothelial cell models of hyperglycemic variability were examined for gene-activating epigenetic changes associated with the chromatinized template using soluble chromatin immunopurification strategies.
Results: We show that specified histone methylases and demethylases are central determinants in the methyl-writing and methyl-erasing events that cause persistent epigenetic changes that are functionally associated with gene regulation. The distinct changes we have identified in the histone code defines a new component of epigenetic control, which could explain why transient elevations of glucose often lead to memory and progressive diabetic vascular complications. Experimental evidence indicates specified changes histone H3 lysine 4 (H3K4) and lysine 9 (H3K9) parallel gene expression in response to transient hyperglycemia.
Conclusions: These studies provide critical insights into the relationship of specified histone signatures. Gene activating events are associated with modifications to the histone tail and the recruitment of enzymes responsible for lysine modification. We also discuss the fate the epigenome may have on metabolic syndrome and future vasculature memories that often end in organ injury and endothelial cell dysfunction.

INV02

Early prevention of macrovascular disease – reason for optimism?

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Cardiovascular disease has now overtaken diabetic nephropathy as the leading cause of premature mortality in young adults with diabetes, and the emphasis on disease prevention has accordingly shifted to a younger age group. There is strong evidence from autopsy, epidemiological and clinical studies that atherosclerosis begins in adolescence in otherwise healthy individuals. Imaging techniques have shown that atherosclerosis develops earlier and is more prevalent in children with diabetes than in age-matched healthy controls, and the progression is more aggressive. Population based studies in children and adolescents with diabetes document high prevalence of cardiovascular risk factors, which is of concern as it is well recognized that CVD risk factors persist or track over time and multiple CVD risk factors tend to reinforce each other. The positive association between poor glycemic control and early development of atheromatosis in type 1 diabetes is well documented. Improved blood glucose control obtained by intensive insulin treatment in adult type 1 diabetic patients is associated with delayed atherosclerosis development and less cardiovascular events. The majority of children and adolescents with diabetes have suboptimal blood glucose control and treatment targets are difficult to reach even with modern intensive insulin treatment. Effective early prevention of cardiovascular disease will involve lifestyle modification. Physical activity and a healthy diet should actively be encouraged, and smoking abandoned. ACE inhibitors should be used in microalbuminuria, and statin treatment may be warranted at an early age. Hypercholesterolemia and hypertension should be actively screened for and treated. Full implementation of existing treatment guidelines may reduce the risk for premature CVD.

ALAD@ISPAD Symposium – A Difficult Start: The Pregnant Adolescent with Type 1 Diabetes Mellitus

INV03

Puberty, ovarian function and pregnancy in adolescents with diabetes

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Insulin is well known for its effects on carbohydrate metabolism, but this hormone also plays an important role in regulating ovarian function. Granulosa, theca and stromal ovarian cells may be affected by insulin deficiency or excess, a frequent pathophysiologic event in women with type 1 diabetes mellitus (T1D). Manifestations of type 1 diabetes mellitus (T1D) on the reproductive system, particularly in women, have suffered dramatic changes during the last few years. Several decades ago, women with T1D frequently exhibited hypogonadism associated with poor metabolic control. Subsequently, as medical treatment of T1D improved, abnormalities of the reproductive system became less frequent, but ovarian manifestations of excessive insulin therapy became more common. Thus, a wide range of reproductive abnormalities, associated with either insulin deficiency or excess, may be observed in women with T1D. Several publications have shown that in spite of intensive insulin therapy, some delay in the age of thelarche, pubarche and menarche is still observed in girls with T1D. In addition, ovarian hyperandrogenism may be observed during late adolescence and an increased prevalence of hirsutism and polycystic ovarian syndrome (PCOS) has been described in adult women with T1D. Recently, we evaluated ovulation in young adolescents with T1D. We observed a similar proportion of ovulatory cycles in girls with T1D compared to healthy controls. A higher ovulatory rate was observed in girls with optimal control compared with those with insufficient metabolic control, but a substantial proportion of ovulatory cycles were still observed in patients with higher HbA1c levels. These data highlight the importance of pregnancy prevention in all adolescents with T1D, regardless of their metabolic control. (Fondecyt Grant 1050452 & 1100123)

INV04

Impact of PPAR natural agonists on the prevention of diabetic embryopathy

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Maternal diabetes increases the risks of embryo malformations, and disturbs feto-placental development and growth. The increased metabolic substrates that reach the intrauterine compartment lead to a pro-inflammatory state evident in the embryo, the fetus and the placenta. Increased reactive oxygen species lead to a loss of essential fatty acids (EFAs), which are highly susceptible to peroxidation. EFAs have important functions as signaling molecules in embryo development. Indeed, arachidonic acid is the substrate for both the synthesis of prostaglandin (PG) E_2, highly needed in the process of neural tube closure, and the synthesis of PGI_2, 15deoxydelta^{12,14} PGJ_2 and leukotriene B_4, respective ligands of the peroxisome proliferator activated receptor (PPAR) delta, gamma and alpha. PPARs are ligand activated transcription factors that regulate metabolic and anti-inflammatory pathways. By studying experimental models of diabetes and pregnancy, we found maternal diabetes alters the concentrations of PPARs and their endogenous ligands in embryos and placentas. Moreover, PPARdelta is highly involved in the embryonic process of closure of the neural tube, PPARgamma mediates anti-inflammatory pathways in fetuses and placentas, and PPARalpha regulates feto-placental lipid metabolism. Interestingly, in pregnant diabetic rats, activation of the three PPAR isotypes with natural PPAR ligands regulates the synthesis of PGs and phospholipids needed in neural tube closure and reduces embryo resorptions and malformations. Besides, dietary activation of PPARs regulates lipid metabolic pathways and reduces matrix metalloproteinases overactivity in the placenta and prevents lipid accretion and reduces lipid peroxidation in the fetus. In conclusion, in maternal diabetes, dietary supplementation with natural PPAR ligands can help to prevent embryo dysmorphogenesis and loss, as well as to regulate pro-inflammatory and metabolic pathways during feto-placental development.

INV05

Impact of maternal nutrition on the short- and long-term offspring outcome

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Low birth weight of infants of adolescent mothers has been associated to inadequate maternal nutritional status, which may exert long-lasting effects on the health of the offspring. We used the rat to study the consequences of maternal undernutrition during the first half of gestation. Control rats (C) were fed ad libitum whereas underfed rats (U) were eat 60% of C from days 0–12 of pregnancy, after which all animals were fed ad libitum. At 20 d of pregnancy, U rats vs. C have higher plasma insulin, glycerol, FFA and ketone bodies but lower fat mass, plasma glucose and insulin sensitivity index (ISI). In U the newborns' number and body wt. and the offspring ISI and insulin-stimulated PTyr-insulin receptor in adipose tissue in 4 month (m) old males were lower. The ISI declined faster with age in male than in females and at 8 month of age it was lower in either U gender than in C. Thus malnutrition during early pregnancy impairs maternal adiposity, enhances maternal insulin resistance, compromises normal foetal growth and accelerates the age-related deterioration of insulin sensitivity in the offspring. To determine the effects of undernutrition during suckling, at delivery other C rats were allow to lactate litters of either 8 (controls, C) or 16 pups each (large litter, LL). From weaning both groups were fed ad libitum, and OGTT at 16 month of age showed that the increase in plasma glucose did not differ between groups but the increase in insulin was lower in LL than in C. Thus, undernutrition during suckling permanently decreases glucose-stimulated insulin secretion without affecting glucose tolerance. In conclusion, experimental animals provides powerful evidence that a dietary insult in utero or during suckling caused by malnutrition programs a permanent abnormal glucose/insulin homeostasis in the offspring, increasing the risk for the development of diabetes in adults. Supported by Spanish Ministry of Science and Innovation (SAF2008-04518).

Avoiding Real Problems: The Threat of DKA

INV06

Cerebral edema and diabetic ketoacidosis – epidemiology and pathogenesis; lessons from the surveillance studies

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Cerebral edema (CE) associated with diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with Type 1 diabetes in the developed world. There has been much speculation about the cause or causes of CE, but since the condition only occurs in around 1 episode in every 100 of DKA, it has been difficult to work out which aetiological factors might be contributing. In the last decade three relatively large case-control studies have been published, where the presenting features and DKA management were compared between cases of children who had DKA with CE and controls who had DKA but no CE. These studies were carried out in the USA, UK and Canada. Results of the studies have shown us that the children most at risk of developing CE, tend to be those with newly-diagnosed diabetes, especially younger children. Those with the most severe acidosis and those with lower PaCO2 levels are at greatest risk, and also those with high blood urea levels, suggesting greater degrees of dehydration. Treatment with larger volumes of fluid during the first 4 hours increased the risk, and although the fluid type was not different, a smaller increase in plasma sodium levels did appear to increase the risk in the US study. Bicarbonate treatment did appear to increase the risk, but not when corrected for the degree of acidosis, making this difficult to interpret. The UK study also found that starting insulin within the first hour of fluid treatment increased the risk four-fold, compared with starting later. None of the studies found that a rapid fall in blood glucose level was a risk factor. These results have implications for the identification of the child at high risk, who can then be monitored and treated quickly if CE should develop. Further, fluid and insulin management has been modified in the latest version of the ISPAD guidelines for the management of DKA in the hope that they will reduce the likelihood of this devastating complication occurring.

INV07

Minimizing the risk of cerebral edema in DKA

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The principal cause of death in children with diabetes is the development of cerebral edema in DKA (DKA-CE). The mortality is 24% with a further 35% morbidity in patients who develop this complication. It occurs almost exclusively as a complication seen in young children and adolescents. Two major theories have been advanced for the development of CE, one being changes in cerebral blood flow leading to vasogenic edema, the second a cytotoxic edema. The suggestion is that DKA-CE is a combination of cerebral ischemia prior to treatment followed by a vasogenic edema that occurs while the fluid deficit is being restored and the hyperglycemia is being corrected. If this hypothesis is correct it supports the concept that a reduction in effective osmolality ($2 \times Na$ + glucose) due to that rapid administration of intravenous fluids and iv insulin may contribute to the development of cerebral edema although this association has not been confirmed in a large retrospective series. There is a hypothesis that it begins with acidosis and hypocapnia causing cerebral vasoconstriction leading to reduced CBF, cytotoxic edema and cerebral injury. The rehydration/reperfusion during iv fluid administration, causes a cerebral hyperemia, reperfusion injury and vasogenic edema. If this is overlaid by breach of integrity of the BBB then an increasingly tenable hypothesis is being built for the pathogenesis of DKA-CE. This might also help to explain the sometimes dramatic responses to the use of hyperosmolar therapy. The guidelines for the initial management of DKA which advise against rapid iv rehydration, in the absence of shock, as well as the gradual reduction of effective osmolality, are congruent with the pathophysiology. Part of the challenge will be to identify those who are developing DKA-CE so that the appropriate change in therapy can be made. CT scans are unreliable because the radiological changes of cerebral edema frequently lag behind a change in the image. The most important monitoring is for signs of CE (headache, vomiting, restlessness, decreased level of conscious) as well as the inability to answer questions. This together with the absence of a rise in serum sodium while the glucose falls during rehydration should alert the physician to the development of CE and lead to institute hyperosmolar therapy.

INV08

Cerebral edema: risk factors in latin america

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Even in our days Cerebral Edema (CE) as a complication of Diabetes Ketoacidosis (DKA) is one of the most prevalent causes of death in childhood diabetes. Different risk factors have been described associated with this painful condition. The traditional risk factors described in the international literature are diabetes onset, age under 5 years, rehydration with hypotonic solutions, severity of acidosis, greater hypocapnia, higher blood urea nitrogen concentration at presentation, treatment with bicarbonate. The frequency of CE is less than 1% in the international bibliography and much higher in Latin American papers. Is there any difference in risk factors of CE in Latin America? Although the publications are few we are able to highlight some particular events related with it. It has been described that lack of social security, low educational level, lack of family support, difficult access, in terms of distance to the nearest hospital, lack of professional training, and specially lack of supplies for control and treatment are related with frequency of DKA- The degree of edema formation during DKA in children may be related with the degree of dehydration and hyperventilation at presentation. Although CE may occur in DKA in children whose medical care meets correct standards the delay in consultation and in the beginning of the treatment would act as a risk factor. The causes and mechanisms of CE are still unknown. CE may be due as much to individual biological variance as to severity of underlying metabolic derangement. DKA prevention and the early diagnosis of CE would be possible in Latin America if access to Health Care System and the proper medical training are improved.

Emerging Trends in Obesity Research

INV09

Insights into the pathogenesis of childhood obesity

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Childhood obesity is the result of a gene-environment interaction. The genetic tendency to have "efficient metabolism" is common among the population yet the prevalence of this trait has not changed drastically within the last decades. While several forms of monogenic obesity have been identified, the vast majority of obese children have a variety of combined predisposing genes along with additional risk factors. On the other hand – epigenetic mechanisms occurring pre-conception, during pregnancy and during the post-natal period have a major impact on the tendency to become obese. Maternal diet and body habitus before and during pregnancy, metabolic derangements during pregnancy such as diabetes, and early post natal growth patterns have all been associated by development of obesity during childhood. Adding these factors to the obesogenic environment commonly encountered in western societies culminates in a myriad of factors that favor the early development of obesity. The obese child is not necessarily ill and may be metabolically healthy, depending on other genes and epigenetic effects that govern lipid partitioning and multiple metabolic pathways related to energy metabolism and substrate utilization.

INV10

Hypothalamic obesity: pathogenesis and natural history

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Craniopharyngioma (Cp), a tumor occurring in the hypothalamic-pituitary area may result in severe obesity. At our centre, approximately 50% develop obesity with the most rapid weight gain occurring in the first 6–12 months postoperatively. Factors related to the development of obesity include evidence of hypothalamic damage on postoperative MRI and higher BMI at presentation. It has been suggested that abnormalities of insulin secretion due to hypothalamic injury may be associated with weight gain in this population. Obese subjects treated for Cp were compared to BMI-matched controls. Metabolic syndrome was more common in Cp than C, and measures of insulin secretion including first and second phase and insulin area-under-the-curve (AUC_{ins}) during OGTT, were significantly higher in Cp. A pilot study to assess the effect of an agent to reduce insulin secretion (diazoxide) in combination with metformin was conducted in 7 subjects treated for 6 months. In the 6 months before treatment subjects gained 9.5 ± 2.7 kg and during the study period this was reduced to 1.2 ± 5.9 kg. AUC_{ins} at study commencement correlated with weight loss while on treatment ($r = 0.82$, $P = 0.02$), indicating that those with highest insulin secretion benefited most from therapy. Exploring mechanisms in uncommon but distinct forms of obesity, such as hypothalamic injury, will help us to better understand the complex regulation of body weight as well as risk for diabetes and cardiovascular disease with the goals of identifying targeted prevention and treatment.

Bad Visions: Substance Abuse in Youngsters with Diabetes

INV11

Smoking and metabolic control

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Smoking is generally recognized and accepted as a major risk factor for the development of vascular disorders in adulthood. Active as well passive smoking are known to affect the cardiovascular system and so does type 1 diabetes. Recent studies showed a higher risk of abnormal glucose tolerance in smoking young adults. The effect of smoking in children and adolescents with diabetes has not yet been studied in detail, but due to endothelial dysfunction pathological changes in lipoproteins, platelet adherence and inflammation of blood vessels are described. Frequency of smoking in adolescents with diabetes does not differ from healthy peer group. Smoking is frequent and common in the young adolescent age group with diabetes, although recent studies showed a significant negative relation of smoking and metabolic control. A multicenter study performed in Europe reported an alarming number of smokers with type one diabetes and described not only higher HbA1c levels in smokers but also unfavorable lipid status and a higher BMI SDS. In combination with diabetes, smoking therefore worsens the cardiovascular risk profile and may aggravate the development of micro- and macrovascular complications. These data are alarming and of major concern as they show that smokers display significantly worse metabolic control. As smoking is an avoidable risk factor for the development of microvascular complications, smoking prevention should obtain top priority in diabetes treatment of children and adolescents. However, in the routine care of pediatric patients with diabetes smoking receives little focus, even in specialized units. Smoking prevention programs and help for smoking cessation need to be initiated in an early age group, at best in childhood and need to be integral part of diabetes education programs. This is underlined by the knowledge that the time point of initiating intervention strategies is essential for success.

INV12

Managing young people with type 1 diabetes in a "rave" new world

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The taxing transition from adolescence towards adulthood frequently intensifies the impact of chronic illnesses, such as type 1 diabetes (T1D), on young patients. It is not uncommon for young people with T1D to exploit recreational drugs as a means for emotional relief and a way of escaping the day-to-day burden of chronic disease. While substance abuse is increasingly encountered in young patients with T1D, especially in the setting of ''rave'' parties, there is a lack of understanding of its impact on glycaemia and the metabolic complications of T1D. In a recent national survey in Australia, 77% of 504 respondents with T1D had used drugs at least once. Two-thirds of users were poly-drug users. Drug-users were similar in age to non-users but reported higher HbA1c than non-users. Two-thirds of drug users had informed their partners about drug use, while only 7% had informed family doctors and/or diabetologists. The modern management of young adults with T1D is incomplete without consideration of drug use, which is currently under-reported and poorly managed even in modern multi-disciplinary diabetes centres. It appears a significant, but currently hidden, contributor to poor glycaemic control and adverse health outcomes in young adults with T1D. With heightened awareness and increased acceptance that poly-drug use occurs, medical personnel should be able to elicit a drug history from patients in a non-judgmental way. Adjustments in therapy could reduce the accompanying metabolic risks. It is time to improve the management of this neglected facet of health in young adults with T1D.

INV13

Substance abuse in youngsters with diabetes addressing risk behavior in adolescents with diabetes

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Introduction: Substance abuse is often the hidden agenda when young people cannot manage their diabetes care appropriately. At the same time medical professionals might lack awareness and skills necessary to identify this problem. This lecture will outline the knowledge, attitudes and skills needed as a first step towards the professional management of this problem.

Objectives: To discuss conceptual differences between explorative behaviours, risk-taking behaviours and problem behaviours in young people with diabetes. To discuss signs and symptoms of possible substance abuse. To discuss communications styles that help identify troubled young people. To discuss communications styles that help young people consider a behaviourial change.

The Loop Club: Is Closing it Near Reality?

INV14

Pumps and sensors from the onset of diabetes

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Objectives: The value of managing children with type 1 diabetes with a combination of insulin pump and continuous glucose monitoring starting from the diagnosis of diabetes has not been determined so far. Therefore, we performed a randomised multicentre study in 5 centres from 4 European countries (Austria, France, Germany, Poland) with a sensor-augmented insulin pump therapy starting at onset of the disease.

Methods: One hundred sixty children aged 1–16 years were randomized to receive insulin pump treatment either with continuous glucose monitoring or with conventional self-monitoring blood glucose measurements. The primary outcome was the level of HbA1c after 12 months. Further analyses included fasting C-peptide, glycaemic variability, sensor usage, adverse events, children's health-related quality of life (QoL) and parent's wellbeing.

Results: HbA1c was not significantly different between the two groups, but patients with regular sensor use had lower values (mean 7.1%, 95% confidence interval [CI] 6.8–7.4%) compared to the combined group with no or low sensor usage (7.6%, 95% CI 7.3–7.9%; P = 0.032). At 12 months, glycaemic variability was lower in the sensor group (mean amplitude of glycaemic excursions 80.2 ± 26.2 vs. 92.0 ± 33.7; P = 0.037). Higher C-peptide concentrations were seen in sensor-treated 12 to 16-year-old patients (0.25 ± 0.12 nmol per liter) compared to those treated with insulin pump alone (0.19 ± 0.07 nmol per liter; P = 0.033). Severe hypoglycaemia was reported only in the group without sensor (4 episodes). QoL parameters were favourable during the study with no differences between the groups.

Conclusions: Sensor-augmented pump therapy starting from the diagnosis of type 1 diabetes is feasible, safe and well accepted in children and adolescents and can be associated with less decline in fasting C-peptide particularly in older children, although regular sensor use is a prerequisite for improved glycaemic control.

INV15

Which roadblocks need to be removed on the way to the closed loop?

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Devices for continuous glucose monitoring (CGM) measure interstitial glucose as a marker of changes in blood glucose. Although still lacking accuracy of blood glucose meters, available devices have improved glucose control. The established technique of continuous subcutaneous insulin infusion (CSII) uses a portable electromechanical pump to mimic nondiabetic insulin delivery, infusing insulin at preselected rates – essentially a slow basal rate throughout the 24 hour with subject-activated boosts at mealtimes. CGM devices and insulin pumps can be combined to form closed-loop systems. Insulin is then delivered according to real-time sensor glucose data, as directed by a control algorithm, rather than at preprogrammed rates. Only a few closed-loop prototypes have been developed and progress has been hindered by suboptimal accuracy and reliability of CGM devices, the relatively slow absorption of subcutaneously administered ''rapid'' acting insulin analogues, and the lack of adequate control algorithms. We believe that these problems can be overcome with commercially available CGM and pump delivery systems in combination with advanced control algorithms such as those based on the model-predictive control. Fully closed-loop may require ultra-fast insulin analogs, dual hormone approaches or novel methods to accelerate insulin absorption such as dermal delivery. Clinical infrastructure to support the use of closed-loop systems will build on existing support for continuous glucose monitors and insulin pumps. This includes training of health care professionals, training of users, and establishment of reimbursement strategies together with health economics assessments. Larger outcomes trials will be required.

The View from the Beta-Cell: A Cure in Sight?

INV16

The view from the beta cell: a cure in sight?

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Exogenous insulin therapy has been, so far, the single approach to treat type 1 diabetes (T1D). Major improvements in insulin peptide activity, insulin delivery devices and glucose monitoring have been observed over the past years. However, it is now well accepted that the cure for T1D and for many cases of T2D requires new strategies targeting the cause of the disease. Beta cell replacement using human islet transplants provides insulin independency but lasting no longer than 2 years. While major advances with microencapsulated porcine islets grafts have been achieved in diabetic mice, its clinical use in humans is far from being applicable. Thus, shortage of donor organs and need for life-long immunesuppression triggered intensive search for alternative cellular sources such as embryonic stem cells (ES) and adult stem/progenitor cells (AS) from different tissues. Genetic reprogramming of mature cells into induced pluripotent somatic cells (iPS) represents a major achievement for regenerative medicine and possibly for the cell-based therapy of diabetes. Collected evidence indicates that adult pancreatic regeneration does occur upon several rescue mechanisms, depending on the physiological needs and injury degree. So, current investigation on beta cell regeneration relies on stimulation of endogenous beta cell proliferation; identification and differentiation of pancreatic progenitors and *in vivo* reprogramming of ductal cells into insulin cell types by means of molecular genetic techniques. Novel approaches using small molecules to selectively regulate stem cell fate are also encouraging. Modulation of the immunesystem and anti-inflammatory strategies inT1D and T2D are crucial therapeutic research lines to solve key pathogenic factors of the disease, hence protecting beta cell mass from ongoing destruction. Further understanding of adult tissues biology and beta cell dynamics will allow for clinical application of cell-based therapies in Diabetes field.

INV17

In situ mhc-i tetramer staining on frozen pancreas samples from type 1 diabetes patients

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Type 1 diabetes (T1D) is characterized by the progressive, immune-mediated loss of insulin-producing beta cells in the pancreas. The definition of T1D as an autoimmune disease has historically been inferred from experiments on peripheral blood samples, showing the presence of beta cell-reactive CD4 and CD8 T cells species and T1D-specific autoantibodies. However, direct association of these autoimmune T cell specificities with pancreatic islets has never been shown. We are taking advantage of the network for Pancreatic Organ Donors (nPOD) which procures freshly frozen pancreas samples from T1D patients and antibody positive pre-diabetic individuals in a coordinated fashion across the United States. In combination with our established *in situ* MHC-I tetramer staining methodology, these samples reveal details on the frequencies and precise histological location of known diabetes-related T cell types. Thus far, three patients have been characterized as suitable candidates for in situ tetramer screening (HLA-A0201 haplotype + presence of CD8 T cell-driven insulitis). All three patients have had diabetes for more than 1 year (1, 3 and 7 years) and show considerable levels of MHC-I expression on most islet cells. We have assayed consecutive sections of each patient using both immunohistochemistry and immunofluorescence staining strategies so as to allow for colocalization with insulin and CD8 and perform correlation on a per-islet basis. Our initial data show the presence of multiple auto-reactive CD8 T cell species per islet, albeit in very limited amounts. CD8 T cells in pancreas sections were probed for reactivity against IGRP, GAD, IA-2, ppIApp and INSB10, with most reactivity found against IGRP. Taken together, we show that the known diabetes-related CD8 T cells specificities in found the blood do act locally at the islet site and that low numbers at any given time point post onset may account for the characteristically slow time course of T1D development.

INV18

Stem cell therapies for type 1 diabetes mellitus

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Type 1 diabetes mellitus (DM1) is an organ-specific autoimmune disease mediated mainly by CD4+ and CD8+ T-cells reacting against islet antigens and causing an aggressive insulitis which destroys the population of insulin producing beta cells and requires exogenous insulin production for life. Acute and chronic conventional dose immunosuppression produces benefit in DM1 but fail to induce long term tolerance when the therapy is stopped. On the other hand, high dose immunosuppression followed by autologous hematopoietic stem cell transplantation (HSCT) induce long term remission in many patients with severe autoimmune diseases other than DM1. Thus, in 2003 we started a phase I/II clinical trial using HSCT in patients 12–35 year old with newly diagnosed (<6 weeks) DM1. Four patients with previous ketoacidosis or receiving steroids pretransplant showed no benefit, but in 21 patients without those conditions insulin could be stopped early after the clinical intervention. Seven of these patients continue to be insulin independent, some after >5 years follow-up, while 14 patients resumed insulin, which could be stopped again (in 2 patients) or converted to low dose (in 12 patients) with the use of sitagliptin. Postmeal C-peptide levels increased in both groups of patients (continuously or transiently insulin-independent). We will also discuss prospectives of treatment of DM1 with other types of stem cells (umbilical, mesenchymal and others).

Looking Healthy: Exercise and Diabetes

INV19

Exercise and metabolic control

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The total amount of physical activity (PA) usually decreases with age in healthy adolescents. According to WHO guidelines, moderate PA is recommended 30–60 minutes daily and sedentary behaviour in front of the TV or computer should be limited. In objective cross-sectional measurements with accelerometry, adolescent girls with type 1 diabetes (T1DM) are almost as active as non-diabetic controls without any association between total amount of PA and HbA1c. In a prospective study the total amount of PA was not associated with changes in HbA1c but with gain in fat free mass. The Hvidoere study group has shown weak associations between PA and HbA1c but stronger and significant associations to psychosocial well-being. Other studies have shown stronger associations between the amount of sedentary behaviour and high HbA1c levels. Exercise has been proposed as one of the cornerstones in the treatment of T1DM and the temporary effect on insulin sensitivity is well documented. However, the documented positive effect of physical exercise on long-term metabolic control and HbA1c levels is limited. On the other hand, benefits on weight control, reduced cardiovascular risk, and improved well-being are much stronger. The occurrence of post-exercise hypo- and hyperglycaemia is a limitation for many patients with T1DM. Education regarding individual adjustments of insulin and diet, in relation to different intensity and duration of exercise with guidance from self control of blood glucose measurements, is the only way how to combine performance of exercise with the aim of achieving a good metabolic control.

Conclusion: Children and adolescents with T1DM should be given the same recommendations regarding physical activity and exercise as their healthy peers. In clinical paediatric practice we should encourage our patients to limit physical inactivity, to stimulate regular daily physical activity and to individually educate participants in sports and exercise activities.

INV20

Algorithms for dose adjustment during exercise

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For children and adolescents with type 1 diabetes, regular physical activity should be a cornerstone of care as it enhances cardiovascular fitness, increases lean mass, improves blood lipid profile, supports psychosocial well-being and health and reduces diabetes-related complications. Compared with sedentary behaviour, being physically active enhances insulin sensitivity and is associated with better haemoglobin A1c (HbA1c) levels in epidemiological studies of youth with type 1 diabetes. Surprisingly, however, clinical trials in which youth with type 1 diabetes undergo aerobic training often fail to demonstrate improvements in HbA1c with regular exercise. This paradox may be explained by the fact that exercise causes increased incidence of hypoglycemia and poor strategies are in place to help youth with diabetes prepare for exercise and competition. Exercise also can cause hyperglycemia, particularly when the event is very vigorous in nature or when there is a high level of competitive stress. This lecture highlights the physiological regulation of blood glucose levels in young people with type 1 diabetes during and after sport, and provides insulin and carbohydrate intake algorithms for dose adjustment during exercise to help limit exercise-associated dysglycemia.

INV21

Exercise and continuous glucose monitoring

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Regular physical activity including moderate competitive sport is beneficial for all individuals and particularly so for people with diabetes. Although these benefits are not disputed in type 2 diabetes, several studies failed to demonstrate any benefit of regular physical activity on metabolic control in type 1 diabetes, with some athletes reported to have substandard metabolic control. Hypoglycemia is very commonly related to exercise and is likely the major obstacle in achieving good metabolic control along with regular physical activity in type 1 diabetes. Real-time continuous glucose monitoring (RT-CGM) is associated with improved metabolic control in children and adults with type 1 diabetes. Randomized controlled trials demonstrated increased time spent in normoglycemia with less glucose variability when using RT-CGM. Low and high glucose alarms along with the predictive trend alarms have the potential to significantly decrease the rate of hypoglycemia related to exercise. If used together with an insulin pump where insulin infusion can be temporarily lowered or suspended, RT-CGM can help maintaining near-normoglycemia without an excessive intake of carbohydrates during and/or after exercise. Finally, modern devices offer an auto-suspend option for suspending insulin delivery at a user-adjustable hypoglycemia threshold. The efficacy of this auto-suspend option in preventing hypoglycemia has yet to be demonstrated in randomized controlled clinical trials. In addition to its effect on metabolic control and glucose fluctuations, the use of RT-CGM with exercise may confer reassurance and an improved image of self-efficacy, both being important factors in preserving good physical condition in conjunction with good metabolic control.

Real Numbers: Data Bases for Pediatric Diabetes Research

INV22

The canadian prospective non-type 1 diabetes study

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Objective: To determine in Canadian children <18 years of age the (1) incidence of type 2 diabetes, medication-induced diabetes, and monogenic diabetes; (2) clinical features of type 2 diabetes at diagnosis; and (3) co-existing morbidity associated with type 2 diabetes at diagnosis.

Methods: This prospective national surveillance study was done in partnership with the *Canadian Paediatric Surveillance Program* and the *College of Family Physicians of Canada - National Research System* and involved the participation of Canadian pediatricians, pediatric endocrinologists, family physicians, and adult endocrinologists. Surveillance occurred over 24 months from April 1, 2006 to March 30, 2008. Incidence rates were calculated using Canadian Census population data and descriptive statistics were used to illustrate demographic and clinical features.

Results: Over the surveillance period, response rates remained consistent at 79% among pediatricians and 96 and 85% among family physicians and adult endocrinologists, respectively. From a population of 7.3 million children, 345 cases of non-type 1 diabetes were reported. The observed minimum incidence rates of type 2, medication-induced, and monogenic diabetes were 1.54, 0.4, and 0.2 cases per 100,000 children aged <18 years per year. Children with type 2 diabetes presented at an average age of 13.7 years and 8% (19/227) presented before 10 years of age. Ethnic minorities were over-represented, but 25% (57/227) of children with type 2 diabetes were Caucasian. 95% (206/216) of children with type 2 diabetes were obese and 37% (43/115) had at least one co-morbidity at diagnosis.

Conclusions: This is the first prospective national surveillance study in Canada to report the incidence of type 2 diabetes in children and the first in the world to report the incidence of medication-induced and monogenic diabetes. Study results provide baseline incidence data based on Canadás unique ethnic, cultural, and geographic characteristics.

INV23

SWEET – An electronic health record for pediatric diabetes reference centers

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''SWEET'' is an acronym standing for´Better control in pediatric and adolescent diabetes: working to create Centers of Referencé and is based on a partnership of established national and European diabetes organizations (www.sweet-project.eu). The SWEET Initiative will work together with technology partners to deliver a platform that allows any participating center to import and input data online using a standard diabetes data set for pediatric and adolescent diabetic patients. Such systems have been implemented in Germany for more than 10 years and have collected data from 15921 pediatric patients with type 1 diabetes. We will provide a specialized Electronic Medical Record system for diabetes management and will also provide a conversion tool to import data to an online platform for data management and site-level reporting. Aggregate data is de-identified and exported to the SWEET project for longitudinal data analysis, health economic data analysis, training and ongoing delivery and improvements in the quality of patient care. Patients will also have the ability to logon to their own secure portal to complete outcomes assessments, receive relevant reminders and education material, as well as communicate with their local pediatric diabetes treatment center. We believe the SWEET initiative and this technology platform will collect the vital data needed to improve care of pediatric and adolescent diabetic patients. Also with the rising health care costs, health economic data are desperately needed to allocate resources appropriately in light of the technological advances in diabetes therapy becoming more widely available.

INV24

The pediatric diabetes consortium

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Although there are some interactions between the major pediatric diabetes programs in the United States, there has been no formal, independent structure for collaboration, the sharing of information and the development of joint research projects that utilize common outcome measures. To fill this unmet clinical and clinical research need, a group of 7 pediatric diabetes centers in the United States has formed the Pediatric Diabetes Consortium (PDC) through an unrestricted grant from Novo Nordisk, Inc. This presentation will describe the organizational structure of the PDC and the design of a study of important clinical outcomes in children and adolescents with new-onset, type 1 diabetes. The outcomes study will describe the changes in A1c levels, the frequency of adverse events (diabetic ketoacidosis/severe hypoglycemia) and the frequency and timing of the ''honeymoon' phase in newly diagnosed patients with T1DM over the first 12–24 months of the disease and examine the relationship between these clinical outcomes and demographic, socio-economic and treatment factors. This project will also allow the Consortium to develop a cohort of youth with T1DM whose clinical course has been well characterized and who wish to participate in future clinical trials and/or contribute to a repository of biological samples. To date more than 600 patients have been enrolled in the study and the target is to enroll at least 1,000 youth with new-onset T1DM. preliminary results will also be presented.

New Approaches to Diabetes Psychology for the Real World

INV25

On the importance of including a psychologist in the diabetes team at diagnosis

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Coping with diabetes in a family is a tremendous challenge. In countries where insulin, strips and education is available free of charge or to a minor expense, psychosocial factors will to a high degree determine the rate of success of the treatment, e.g. the risk for acute and long-term complications of the child. In societies with less economic support of the family the diabetes diagnosis of the child can throw the family into poverty. Even though paediatric care is traditionally family-oriented, family-system thinking can be problematic to implement, both within the team and at the clinic. The psychotherapist should meet the family, preferable together with the paediatric diabetologist, as soon as possible after the diagnosis. Then the family members can easily accept the psychologist as a member of the diabetes team. The role of the therapist is at least dual. The family is to be helped in the crises reaction and to find favourable coping strategies but the task is also to support the other members of the team in their work with the family. The role of the paediatrician and the diabetes nurse in encouraging and supporting families of a child with a chronic illness may also become an obstacle for the parents to talk about difficulties. An experienced psychotherapist, who also can modulate the physician's tendency to give a rapid, ''expert'' answer, can bridge this gap. Commonly, the most constructive solution to a given problem is to support the family's approach or, when necessary, help them to choose another strategy. The ultimate goal is to promote healthy family coping strategies at diagnosis and forward to optimize the chances for a high quality of life for the child.

INV26

Youth-parent interaction as an intervention target

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Research over the past three decades has shown that youth-parent interaction in general and around diabetes management specifically are important processes affecting outcomes such as glycemic control, treatment adherence, quality of life and psychological adjustment to diabetes. The primary conclusion from this body of research is that youths with type 1 diabetes who enjoy continued parental involvement and collaboration in diabetes management throughout adolescence are substantially more likely to achieve and maintain more favorable diabetes outcomes, while those with conflictual or neglectful relationships with parents are at high risk of poor glycemic control, psychological complications and excess helath care utilization. An additional conclusion is that behavioral interventions targeting these processes have shown considerable promise, but that dissemination of these interventions into widespread clinical practice is a major challenge. This research supports the argument that the family is the most appropriate locus of treatment in pediatric diabetes and that promotion of healthy and constructive parent-adolescent teamwork around diabetes management should be a central goal of treatment. This presentation will review the evidence base supporting these conclusions, with an emphasis on the most recent research that has yielded more detailed and specific information about key interaction processess and characteristics, as well as controlled trials of pertinent behavioral interventions. Despite the world-wide epidemic of type 2 diabetes in youth, there have been very few parallel studies of that clinical population, which may differ in important rspects from the type 1 population. The implications of these findings for clinical management and education of families of adolescents with diabetes will be discussed and recommendations offered.

INV27

Discussing health-related quality of life with adolescents

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The ISPAD clinical practice consensus guidelines recommend that professionals with expertise in the mental and behavioral health of children and adolescents (e.g., psychologists and social workers) should be available for inclusion within the diabetes healthcare team, with a goal to improving effective self-management and psychosocial functioning of the whole family. Nevertheless, these specialist resources are not always available, so it is important to consider other ways to encourage assessment of psychosocial function with or without the availability of specialists in this area of care. Systematic assessment of the needs of youth with diabetes and their families is an important starting point in the provision of appropriate psychosocial support. Psychosocial evaluation tools can be used to assess the psychosocial needs of the young person and family and identify possible barriers to effective self management. Problem areas can then be defined and an action plan developed to improve diabetes control and overall quality of life. The use of valid psychosocial evaluation methods has been shown to be effective. Our group confirmed in a randomized controlled trial that regular monitoring and discussion of health-related quality of life (HRQoL) improves the psychosocial well-being and satisfaction with care of adolescents with type 1 diabetes. However, withdrawing the formal assessment of HRQoL resulted in the disappearance of those positive effects and a deterioration of glycemic control. Within the DAWN MIND Youth initiative we currently aim to facilitate improved use of assessments of self-management, family function, and QoL as an essential part of routine appointments with healthcare professionals, regardless of whether they have extensive psychological training. The ultimate aim of this is to establish a new standard for pediatric care, under which any clinical encounter is based on a thorough understanding of each child and family's psychosocial needs.

Early Complications: A Nutritional View

INV28

Nutrition and microalbuminuria

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Microalbuminuria is the best predictive marker for future development of nephropathy in people with type 1 diabetes. Improved glycemic control, lowering of blood pressure and maintenance of a healthy body weight are essential for reducing the risk of nephropathy. Medical nutrition therapy has been demonstrated to be effective in achieving reductions in HbA1c and cardiovascular risk factors, which in turn, may assist in delaying the progression to nephropathy. In addition, there is evidence that avoidance of a high dietary protein intake slows the progression of nephropathy. Questions remain about the best approach to dietary management in young people with microalbuminuria. The food choices of adolescents should provide sufficient energy and nutrients for optimal growth and development, with total daily energy intake distributed as Carbohydrates: more than 50%, Protein: 10–15% and Fat: 30–35%. Recommended protein intake decreases during childhood from approximately 1 g/kg/day for a 10 year old to 0.8–0.9 g/kg/day in later adolescence. When persistent microalbuminuria occurs, excessive protein intake may be detrimental. It is prudent to advise that intake should be at the lower end of the recommended range. There is insufficient evidence to restrict protein (<0.8 g/kg/day) and such restrictions may have deleterious effects on growth. Adult studies provide evidence that changing the type of protein, notably red meat to vegetable protein, may also reduce the risk of nephropathy. Therapeutic trials are required to examine the effects of different types of protein. Moreover, some studies have supported the role of dietary fat intake in the development of nephropathy. Interventions to prevent or slow decline in renal function should include individualized nutrition therapy to optimise glycemia, weight and lipid levels; moderation of protein intake and if feasible, substitution of vegetable or fish protein for animal protein.

INV29

Nutrition and hypertension

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Hypertension and diabetes mellitus (DM) are frequently associated, and this co-existence seriously affects both morbidity and mortality. Subjects with DM and hypertension are at high risk for both macro and micro-angiopathy. Among youth with DM, elevated blood pressure represents one of the most common co-morbidities. A recent study suggests that 30% of children 10–19 years of age with type 1 or type 2 DM have high blood pressure, particularly those with type 2 DM (6.8 and 36.6%, respectively). In type 1 DM, the development of high blood pressure is related to nephropathy. In type 2 DM, hypertension is rather a co-morbidity which may be present at diagnosis or appear earlier in the course of the disease. Obesity, particularly central, is a strong independent risk factor for hypertension. In the last 20 years the increase in childhood obesity has been associated with a higher prevalence of type 2 DM in youth and the appearance of a picture characterized by the co-existence of characteristics of type 1 and type 2 DM, the so called ''double'' or ''hybrid'' DM. Nutrition represents a central part in the management of youth with DM and hypertension. It has been suggested that a diet rich in vegetables, fruits and low-fat dairy may be inversely related to hypertension, at least in type 1 DM. Current data appear to indicate that adolescents with type 1 DM consume fewer calories from carbohydrates but more calories from fat than adolescents without diabetes and exceed the recommended levels of fat intake. As sodium excess in diet can be related to an increase in blood pressure, current ISPAD Clinical Practice Consensus Guidelines recommend less than 6 grams/day of salt (sodium chloride). The management of obesity as well as the importance of a healthy life-style in the pediatric population should be through collaborative efforts among the patient, family, physician, behavioral specialist, dietitian, nurse educator and school.

INV30

Nutrition and dyslipidaemia

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Atherosclerosis begins in childhood. EDIC demonstrated in type 1 diabetes (TID) that hyperglycaemia drives atheroma, a process mediated largely through chronic kidney disease. Periods of insulin deficiency also lead secondarily to elevated triglycerides, and atherogenic LDLc. Dyslipidaemia has been reported in young people with T1D from USA, Europe and Bangladesh. Nutrition also plays a significant role and many children with diabetes consume an atherogenic diet. Moreover, associations exist between children who skip meals and suboptimal HbA1c, overweight and high LDLc. Children with T1D are more overweight than matched peers and may have increased intra-abdominal fat. Occurrence of the metabolic syndrome in young adults with T1D is associated with a 2.5 fold increased risk of cardiovascular and diabetes mortality compared with non-diabetic peers. The often overlooked presence of familial hypercholesterolemia exacerbates any dyslipidaemia. Primary prevention should begin in children with diabetes by annual lipid screening. The main goal of treatment is to reduce atherogenic risk factors with a particular focus on reducing LDLc. In a paediatric environment dietary changes are preferable as first line treatment to pharmacological intervention and functional foods containing plant sterols and stanols reduce LDLc. The Dietary Intervention Study in Children (DISC) demonstrated the efficacy and safety of low total and saturated fat diets in prepubertal children with elevated LDLc over 7 years of followup. Despite a paucity of data from large prospective studies, statin therapy has been shown to be effective in T1D. Therefore, after glycaemic control has been optimised and with dietary management and weight reduction, if LDLc levels do not reach target of LDL <2.6 mmol/l (100 mg/dl) pharmacological therapy should be considered. Caution must be used in females who may wish to become pregnant. Elevated triglycerides will improve with weight reduction and glycaemic control.

On the Lookout for the Right Target: The Current Situation of Diabetes Prevention

INV31

Should we target viral disease to prevent diabetes?

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To date, prevention strategies for type 1 diabetes (T1DM) have been largely unsuccessful. This may be because secondary prevention – which involves suppression of autoimmune mediated pancreatic beta cell destruction after the appearance of islet autoantibodies – are implemented too late in the pathway towards clinical disease. In contrast, primary prevention may successfully lead to T1DM prevention, however it is essential that the initiators of beta cell autoimmunity are better understood. Of the putative environmental factors involved in the initiation and acceleration of beta cell autoimmunity, viral infections have received most attention. There is substantial evidence supporting a causal role for enterovirus infection at T1DM onset, based on studies using molecular methods for viral detection. Genetic predisposition may mediate the risk for a viral trigger, with protection from disease afforded to individuals with variants of IFIH1, which mediates induction of interferon response to viral RNA (1) and a greater risk of an enteroviral trigger amongst individuals with low risk HLA genotypes (2). The most compelling evidence is positive immunostaining for enterovirus capsid protein in 61% of pancreatic autopsy specimens from patients with recent onset T1DM (3). However, longitudinal studies of at risk children have demonstrated less consistent evidence for an association between islet autoimmunity and viral infections. Rotavirus infection may also modify the risk of islet autoimmunity, but only one group has demonstrated an association between rotavirus infection and islet antibody seroconversion in children at risk of T1DM (4). The body of evidence supporting a role for viral infections in T1DM is comparable to, if not greater than, the evidence for the first primary prevention study (TRIGR). However, prevention studies against viral infections require development of vaccines that target 'diabetogenic' genotypes, they must be adequately powered, collaborative, with a multicenter approach, and target at-risk individuals – a population that has become less well defined in recent years (5).

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INV32

Immunosuppression studies aimed at interdicting and preventing type 1 diabetes (T1DM)

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A range of immunosuppressive and immunomodulatory medications have been investigated for the control of autoimmunity and the preservation of β-cell function in T1DM. While some of these agents have been hindered by limited efficacy and/or safety/tolerability concerns, others have shown promise, including a number of medications used in the treatment of other immune-mediated conditions. Among the agents currently being investigated for efficacy in T1DM intervention are the autoantigen glutamic acid decarboxylase 65 (GAD65) and a number of non-antigen specific therapies, including DiaPep277, anti-CD3 and anti-CD20 monoclonal antibodies, Cytotoxic T-Lymphocyte Antigen-4 immunoglobulin (CTLA-4 Ig), Anti-Thymocyte Globulin (ATG) +/− Granulocyte Colony Stimulating Factor (GCSF), alpha-1 antitrypsin, autologous umbilical cord blood (UCB) infusion combined with docosahexaneoic acid (DHA) and vitamin D3, and dendritic cells (DC), and mesenchymal stem cell (MSC) therapy. Given the complexity of the T1DM disease process and the limited success obtained with monotherapy, evidence suggests that combination therapy will likely be the best approach to future T1DM interdiction. This strategy has the potential to act on multiple targets with potentially synergistic mechanisms of action. Further, the use of multiple agents at lower doses may achieve higher efficacy with a reduced risk of adverse effects; the success of similar approaches has been demonstrated in both cancer and HIV treatment. However, as new T1DM treatment modalities are explored, important factors will need to be considered during trial design include target patient populations, screening requirements, ease of agent administration, existing efficacy and safety data, and costs.

INV33

C-peptide as surrogate therapeutic marker for a successful outcome

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Numerous studies have highlighted the relevance of residual beta cell function measured by fasting and stimulated C-peptide in patients with Type 1 diabetes (T1D). In particular patients who maintained a C-peptide secretion >0.2 nM few years after diagnosis show better metabolic control as evaluated by HbA1c and a reduced risk of developing long term complications. Immune intervention soon after clinical diagnosis of T1D to protect residual beta cell function is therefore a field of great and increasing interest. Ongoing trials currently use C-peptide measurement as the main end point parameter for an effect of a given treatment. The absolute C-peptide levels reached as an indicator of residual B-cell function as well as the percentages of T1DM patients achieving a certain fasting and stimulated C-peptide endpoint 1 or 2 years after diagnosis vary considerably between studies. This is due to a number of critical factors including, among the most relevant ones, age at disease onset, basal and stimulated C-peptide response at diagnosis, genetics including human leukocyte^2 antigen (HLA) genotype, sample size, severity of metabolic decompensation at diagnosis, presence of insulin resistance, insulin usage and whether near-normal glycemia (with HbA_{1c} consistently <7%) is obtained with intensive therapy, which may strongly influence the outcome of the therapeutic intervention. A number of studies reported a short-term increase of the secretory response. If this transient improvement is due to an actual increase in insulin secretion by the repair of B-cell mass and/or function or rather just to the correction of precipitating factors is not clear. At present there are no definitive indicators that identify individuals with a slow versus a more rapid loss of insulin secretion over time and the factors that may predict these changes remain to be better investigated prospectively. There is clearly the need to know more about the natural

decline of C-peptide in T1D from diagnosis over the years in patients diagnosed at different age (before or after puberty) independently of any treatment. A real picture can only be obtained through the collection of a large number of T1D patients with different characteristics at onset as indeed is the case in an heterogeneous disease such as T1D.

Ethical Viewpoint: What are the Limits of Pharmacological Intervention in the Paediatric Patients with DM?

INV34

Interventions in the context of difficult psychosocial situations

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Conflict can exist between the scientific search for truth by clinical trials and the ethical duties to protect participant welfare. Justice, beneficience, non-malaficience and autonomy are guiding moral principles for ethical decision making. For younger children, decisions are invested in the parents/guardians and medical personnel. Older children and adolescents must be involved in the decision. Decisions vary and depend upon relationships between the various role players, the validity and applicability of the research and perceived benefits of the research. In difficult psychosocial situations these factors are accentuated. Poverty, access to care and new technology, improvements in quality of care, sustainability of interventions and understanding at individual and societal levels are considerations when evaluating interventions. The´standard of caré in poor socio-economic conditions, especially in relation to diabetes interventions, are not the same as in developed economies. Sustainability and applicability of new interventions have to be considered to ensure that guiding moral principles are met. The right to make judicious and autonomous decisions regarding participation in interventions depends on the ability to weight risks and benefits of the intervention. In difficult psychosocial situations this ability needs to be carefully assessed. This presentation shall explore these issues.

INV35

Global inequalities and pediatric research

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Global inequality has been a great issue in many fields. Globalization around the world does not bring equal outcomes in developed and developing countries. This also applies in medical research, which in return will bring a better patient care. Research in children needs special attention as we have to move forward toward better care for children with any disease. Unfortunately the quantity and quality of research in different countries are grossly unequal. As economic inequalities exist between countries, the quantity and quality of research held in different places also become unequal. While the majority of children live in developing world, there are only several sufficient data available about the exact prevalence or incidence of diseases as a result of underdevelopment of research in such countries. Another factor that create inequalities of research are research fund. In 1990, The Commission on Health Research for Development had found the concept of ''10/90 Gap''. At that time, only 10% of the money spent worldwide on health research was focused on the health problems of 90% of the global population. The Programme for Global Paediatric Research (PGPR) was then created in 1998. But after a decade from the founding of PGPR, there is still disproportionate quantity of scientific research between developed and developing countries. For example, in America or England, many papers of diabetes research are published per year. In contrast, less than 10 manuscripts of diabetes studies are published in Indonesian Pediatric Journals from the period of 2001–2010. Although inequalities in many fields could not be erased in a matter of years or even decades, we can move toward these barriers by doing research together between developed and developing countries. It needs long process of collaborating between countries or research centers, and many steps have to be made. But the greater the effort, the more we can gain to cater our patients needs globally.

INV36

Parents views on screening and prevention of diabetes versus child autonomy

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Determination of auto-antibodies can be used to predict Type 1 diabetes (T1D), in first degree relatives and in the general population. By identifying high risk individuals it is possible to prepare the family so that they recognize symptoms early if the disease becomes manifest, and thereby dangerous clinical manifestations can be avoided. On the other hand a number of individuals and families will be worried, of whom most would never have got diabetes. Therefore the opinion not to inform, if at all screen, has been common. ABIS (All Babies in Southeast Sweden) is a cohort of 17 000 children followed from birth between 1st of Oct 1997–1st of Oct 1999. As one of the aims is prediction of Type 1 diabetes we have asked parents in questionnaires, both identified and anonymous versions, about their views on information, their role as parents contra the autonomy of their child. A majority of parents have meant that they want to be informed about results, eg increased risk of their child of getting diabetes, even in case there is no prevention to offer. A majority has had the opinion that still when their child is 8–9 years old, it is the right and duty of parents to take the responsibility and decide if their child should be screened and when information should be given. With increasing age of their child they are prepared to listen more to his/her opinion, and as teenager gradually let her/him be part of the decisions. In one study (4000 families), 66% were positive providing information to the child and of them 70% thought that children should be allowed to decide about blood-sampling procedures , but to a less extent about participation (48.5%), analyses of samples (19.7%) and biological bank storage (15.4%).

Conclusions: A majority of parents, at least in Sweden, are positive to participating in screening for Type 1 diabetes. Of them a majority wants to be informed about results. The autonomy of the child has to be adapted to its maturity and understanding.

INV37

New regulations in the EU and their implications on research in children

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Off label use of drugs in the pediatric population is associated with a higher risk for adverse reactions. Age adjusted dosages are unknown and the introduction of drugs in the pediatric

population based on adult use, is doubtful. Not only PK/PD responses may differ in the pediatric population, but safety nor efficacy are guaranteed. This may be unethical and with unacceptable risks. Since 2007, prior to marketing authorization for new drugs in the EU pharmaceutical companies must provide results of pediatric studies, performed according to a pediatric investigation plan (PIP). The same also applies to authorised products with a valid patent, when a new indication, form or route of administration is sought. These obligations will translate into an increased number of industry-sponsored clinical trials in this population. In *Ethical Considerations For Clinical Trials On Medicinal Products Conducted With The Paediatric Population* a minor increase over minimal risk is accepted when a possible advantage may be expected for children with specific diseases. As discussed by Westra et al, this may be considered inconsistent with the European Convention on Human Rights and Biomedicine, stating that this research is only acceptable with minimal risk and minimal burden. Harmonisation of terminology is requested to identify and apply European recommendations. Then drug prescription in children can be based on a sound evaluation of their benefit/risk ratio in particular age/disease groups. Limited availability of paediatric patients may pose recruitment issues (eg type 2 diabetes or hypertension), and for which many medicinal products are under development. This imposes collaboration between different centres on different sides of the world. Therefore paediatric networks will be necessary.

Conclusion: Off-label use of drugs in children is unethical and unacceptable. It will be a challenge to find the optimal way to minimalise risk and optimalise benefit for this population.

Looking at the Genes – New Insights

INV38

Neonatal diabetes and pancreatic hypoplasia

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Neonatal diabetes or monogenic diabetes of infancy can manifest as a transient or permanent condition. TNDM is most commonly caused by imprinting disorders on chromosome 6q24 (TNDM1. Uniparental Isodisomy Chromosome 6, Paternal Duplication of 6q24, loss of maternal methylation). Recently it has been identified that over half of those with maternal hypomethylation at 6q24 have relaxed maternal methylation at other imprinted loci and that the majority of these patients have mutations in transcription factor *ZFP57*. Transient neonatal diabetes has also been described with mutations in the genes encoding the ATP-sensitive potassium channel *ABCC8* (TNDM2) and *KCNJ11*(TNDM3). TNDM1 is characterised by third trimester IUGR, low birth weight and very early onset diabetes. Treatment is usually with insulin but remission occurs within 3 months with a liability to relapse in adolescence or early adulthood. PNDM is a more diverse condition with an unknown genetic cause in about 40% of cases. Diabetes may be caused by defects in pancreatic development (*IPF-1*, *GLIS3*, *PTFA1*, and most recently *NEUROD1*: the latter two having severe cerebellar hypoplasia), defects in Beta cell function (*KCNJ11*, *ABCC8*, homozygous Glucokinase inactivating mutations) or increased islet cell destruction (*INS* and *EIF2AK3* by apoptosis and *FOXP3* by the only autoimmune condition causing neonatal diabetes). Whilst the effectiveness and diversity of treatment is very dependent on associated organ damage accrued from the diverse mutations, *KCNJ11* and *ABCC8* mutations are remarkable as one of the first successful examples of pharmacogenetics: identification of patients with these mutations causing neonatal diabetes led to many being successfully transferred from a previous lifetime of insulin therapy with relatively poor glycaemic control to excellent control on oral sulphonylureas. With the rapid advances in molecular biology techniques more causes of permanent neonantal diabetes are likely to be identified soon.

INV39

How to approach monogenic diabetes of unknown etiology

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In recent years there has been significant progress in defining the genetic aetiology of neonatal diabetes (NDM). It is likely that all cases result from a single gene disorder since markers of autoimmunity associated with polygenic type 1 diabetes are rare in patients diagnosed before 6 months. Activating mutations in the *KCNJ11* and *ABCC8* genes encoding the Kir6.2 and SUR1 subunits of the beta-cell ATP sensitive potassium (K_{ATP}) channel are the most common cause of neonatal diabetes, accounting for around 40% of case. The majority (~90%) of patients can achieve improved glycaemic control on high dose sulphonylureas. *INS* (insulin) gene mutations are the next most common cause of NDM; either recessive loss of function mutations or dominantly acting mutations that affect folding of the proinsulin molecule with consequent endoplasmic reticulum stress. Animal models can inform the search for new genetic aetiologies and the development of next generation sequencing technologies provides exciting possibilities for large scale sequencing studies. The identification of specific genetic subtypes of neonatal diabetes not only provides accurate information regarding inheritance and prognosis, but can inform treatment decisions and improve clinical outcome.

