Pediatric Diabetes
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INVITED SPEAKERS

Prevention of type 1 diabetes – Is it possible?

INV1
Lifestyle and insulin resistance: prevention strategies for type 1 diabetes

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Insulin resistance (IR) has entered the field of childhood diabetes over recent time because of the rising incidence of childhood obesity, but the association was always there. The early reports from Harold Himsworth are often misconstrued to mean that IR distinguished adult from juvenile onset diabetes, but that was not the case. Elliott Joslin saw little utility in IR as a means of separating young from old and, as recently as 1982, De Fronzo, reported IR as '. . . ..a common feature of T1D'.

The possibility that insulin resistance might drive diabetes in childhood, as it is widely understood to in adulthood, has been incorporated into the 'accelerator hypothesis' and, to a greater or lesser extent into the 'overload hypothesis' (Dahlquist) and 'double diabetes' (Libman and Becker). Weight excess is the commonest single cause of IR, though a rise in IR for whatever reason might be expected to stress the beta cell, which is considered to underpin diabetes generally.

Lifestyles have changed in many different ways over the past 30 years, during which childhood diabetes has tripled, and if insulin resistance is to become a serious contender, the mechanisms involved must be understood before a plan for prevention can be rationally formulated.

Trials of immunotherapy, based on the autoimmunity paradigm for childhood diabetes, have proved disappointing, and have not so far brought human benefit. Evidence for the 'coxsackie' hypothesis, the 'hygiene' hypothesis, and the 'whipworm' hypothesis has been difficult to pin down in humans, and care must be taken not to overinterpret their success in the NOD mouse, where immunotherapy initially looked so hopeful. The 'cow's milk' hypothesis is under human trial at present (TRIGR) but, again, care must be taken in its immunological interpretation not to confound the extra weight and height gain that result from formula feeding. Both are independently associated with IR, and children who develop T1D are heavier than those who do not.

INV2
Nutritional agents in the prevention of type 1 diabetes

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Objectives: Accumulated evidence supports a crucial role of environmental factors in the development of type 1 diabetes (T1D). This presentation sets out to critically assess the impact of dietary factors, such as intake of foreign proteins, fats, and vitamins in the pathogenesis of T1D and the potential of dietary interventions in disease prevention.

Methods: Published and unpublished data on the contribution of dietary factors to the development of T1D and the outcome of dietary intervention studies are reviewed.

Results: Whether breastfeeding protects against T1D or not has remained a controversial issue. Early introduction of cow´s milk-based formula may increase the risk of T1D. Similarly early introduction of cereals has been implicated as a risk factor for T1D. A Finnish study has indicated that early introduction of fruits and berries as well as roots in infancy increases the risk of subsequent T1D. Some investigations have suggested that the lack of vitamin D supplementation in infancy increases the later risk of T1D. The use in infancy of cod liver containing both vitamin D and omega 3 polyunsaturated fatty acids has been observed to be associated with a decreased T1D risk, but this could not be confirmed in a larger study. The TRIGR study, the only properly powered primary prevention trial in T1D, tests whether weaning to an extensively hydrolyzed formula decreases the incidence of T1D in high-risk children. The final endpoint will be reached in 2017. A pilot study with a gluten-free diet in the first years of life found no difference in signs of beta-cell autoimmunity in children at risk. The FINDIA study, another pilot, indicated that weaning to a formula free of bovine insulin reduced the cumulative incidence of autoantibodies with around 60% by the age of 3 years.

Conclusions: No specific dietary factor or nutrient has so far been shown unequivocally to play a role in the development of T1D. More research is definitely needed in this field.

INV3
The environmental determinants of diabetes in the young (TEDDY) and prospects of prevention

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Autoimmune (type 1) diabetes (AI-DM) is a multistage disorder. Children are born genetically predisposed to develop islet autoimmunity. Unknown environmental exposures may trigger islet autoimmunity mediated by autoantigen presentation on specific HLA class II heterodimers. Islet autoimmunity is marked by autoantibodies against insulin, glutamic acid decarboxylase (GAD65), IA-2, or the ZnT8 transporter. The autoimmunity stage is thought to involve CD8+ T cells recognizing HLA class I molecules on the beta cells. Progression to clinical onset of diabetes is highly variable. Time to onset is related to the number of islet autoantibodies. In the TEDDY study, 8686 children with high risk HLA-DQ (2/8, 8/8, 4/8, and 2/2) are followed from birth until 15 years of age. Environmental exposures for either islet autoantibodies and progression to onset are analyzed. More than 40 non-HLA genetic factors are also analyzed. It remains to be clarified to what extent HLA-DQ and the non-HLA genes contribute to the initiation

of the chronic islet autoimmunity, progression to diabetes, or both. TEDDY data indicate that unknown environmental exposure(s) trigger islet autoimmunity already at 1–3 years of age. In 1–8 years of TEDDY children more than 400 developed islet autoimmunity but only 150 have progressed to diabetes, so far. Hence, prevention may be approached at three different stages. Primary prevention would be treatment of individuals at increased genetic risk. TRIGR is testing if hydrolyzed casein milk formula reduces diabetes and PrePoint if oral insulin prevents insulin autoimmunity in genetically predisposed infants. Secondary prevention in subjects with persistent islet autoantibodies already involves non-autoantigen-specific therapies, such as anti-CD3 monoclonal antibodies, or autoantigen-specific therapies, including insulin or recombinant human GAD65. Poor results so far, leaves insulin replacement therapy as the only alternative at the clinical onset of diabetes.

Team-work in diabetes

INV4
What do we know about the value of team-work in diabetes?

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While promoting effective and safe pediatric diabetes care is a universal goal, clinical teams managing children and young people with diabetes and their families vary considerably in their approach. Substantial variations in the quality of diabetes care offered across centers and countries are identified in several studies. Determinating how much of the variation reflects differences in organizational structures and principles that affect the quality of services, staffing, professional training, and education, rather than unmeasured variations in medical care, can be challenging. Given the complexity of the disease and the importance of managing all aspects of care a deeper knowledge of team functioning and coordination of care are needed to identify relationships between inputs, structures, quality, and resource use.

INV5
How can team collaborate to achieve an improved outcome?

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Differences in mean HbA1c between different diabetes pediatric centers have been found and clinicians experience shows that it is also difficult to implement national guidelines in the practical everyday work. Studies within other medical specialties have shown that systematic quality improvement collaborative in combination with national quality registers can improve clinical results. Twelve pediatric diabetes teams in Sweden participated in a quality improvement collaborative aiming to improve the quality of pediatric diabetes care. The Swedish pediatric quality registry, SWEDIABKIDS was used as a tool and resource for outcome measure. The collaborative included learning about, and working with, systematic improvement methods, e.g., the PDSA wheel to test different improvement ideas. Each team defined treatment targets, areas needing improvement, and action plans.

The mean HbA1c level was reduced already at 6 months after the start of the collaborative program, but even more pleasing was that also the long-term follow-up, after another year, confirmed the sustainability of the results. The mean reduction for all was 3.7 mmol/mol, $p < 0.001$. The frequency of severe hypoglycemia and/or ketoacidosis and was also reduced. Change concepts were for example improved guidelines, reception planning, information to the patients, improved teamwork and use of the registry, and health promotion activities.

Many children benefit from the improvement and, if the results are sustainable, run less risk of late complications. The results emphasize how important it is for health professionals to work continuously and systematically to improve the treatment, structure and processes of care. By involving pediatric diabetes teams in a quality improvement collaborative together with access to a quality register, quality of pediatric diabetes care can improve and thereby contribute to reducing the risk of late complications for children and adolescents with diabetes.

INV6
How to start up a pediatric diabetes center and diabetes teams when there are none. The Kenyan experience

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From the World Bank records, 72% of deaths due to chronic diseases occur in low income countries. In Kenya, available statistics indicate a diabetes prevalence of 3.5% of the population. Due to the high burden of infectious deceases especially malaria and HIV, childhood diabetes was not a priority disease in Kenya. The situation is aggravated by patient's inability to buy insulin due to poverty.

We started a Peadiatric Diabetes Centre at Kenyatta National Hospital (KNH), Nairobi in 2009. Prior to the Centre, KNH had a diabetes clinic once a week with an annual patient load of 15 000 for both children and adult patients. Only mixtard insulin was available, the patients did not have glucometers and blood and urine sugars were done only on the day of the clinic. Due to the large number of patients the consultation could not last more than a few minutes, even those involving children.

A study done at the Kenyatta National Hospital (KNH) in 2005 showed that 29.8% of the patients in diabetes ketoacidosis died within 48 h of presentation. A 2004 Tanzanian study showed that 50% of the deaths in patients on insulin were due to diabetic ketoacidosis. These studies helped us prioritize the patients' needs at the Centre. As a first step, we separated the children from the adults. In parallel, the Paediatric Endocrinology training Centre for Africa was launched to train doctors on pediatric endocrinology and with this came in ISPAD and ESPE team. The Centre currently attends to about 200 children coming predominantly from Nairobi and its neighborhoods. We now have several pediatric diabetes clinics, educated several health care professional, free insulin, and soon free glucometers and glucose strips for the children. A senior nurse in KNH is currently undergoing specialized training in South Africa. Our major challenge is how to expand these services to areas outside Nairobi given the high number of people who cannot afford bus fare and diabetes care services.

Insulin in the neonate and infant – Not enough or too much?

INV7

Congenital hyperinsulinism: genes, phenotype, treatment, and reversion to diabetes

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Objectives: Congenital hyperinsulinism (CHI) is a rare, heterogeneous disease resulting in hyperinsulinemic hypoglycemia, formerly known as leucine-sensitive hypoglycemia, nesidioblastosis, and persistent hyperinsulinemic hypoglycemia of infancy. Since 1994, an explosion of knowledge has improved the disease management.
Methods: DNA sequencing, clinical data, 18F*-Fluoro-DOPA PET-CT scan, histology, and review of the literature.
Results: In more than 400 children with CHI from many countries, mutations were found in six different genes, *ABCC8*, *KCNJ11*, *GCK*, *GLUD1*, *HNF1A*, and *HNF4A*. Three had paternal uniparental disomy of chromosome 11p and Beckwith–Wiedemann syndrome. No mutations were found in U*CP2*, *HADH*, or *SLC16A1*. Clinical onset varied from day 1 of life to adulthood. At our center, 18F*-Fluoro-DOPA PET CT was performed in 24 children, of which 6 (25%) had histologically verified focal CHI and cure after restricted pancreatic surgery. In patients with subtotal pancreatectomy, one child had both hypoglycemic and hyperglycemic episodes; the rest had normal glucose levels, none had malabsorption. One child reverted spontaneously to diabetes at age 14. Brain damage was occasionally profound after longstanding hypoglycemia.
Conclusion: Due to the complexity and heterogeneity of CHI, individualized patient management on an expert level is recommended to prevent brain damage and diabetes, however not always avoidable. In HNF1A-CHI and HNF4A-CHI and other rare cases, spontaneous reversion to MODY may occur.

INV8

Treatment of neonatal diabetes: insulin and sulfonylureas for an holistic treatment approach

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Background: Neonatal diabetes mellitus (NDM) is a rare genetic form of pancreatic beta-cell dysfunction leading to hyperglycemia early in life. We evaluated phenotype-genetic subtypes correlations and clinical outcome in a cohort of patients with NDM diagnosed before the age of 1 year, without beta-cell autoimmunity and with normal pancreas morphology.
Methods: We prospectively investigated patients from 20 countries referred to the French NDM Study Group from 1995 to 2010, for associated genetic abnormalities: alterations in the 6q24 locus and in the genes encoding the K_{ATP} channel (*ABCC8* and *KCNJ11*) and preproinsulin (*INS*).
Results: We identified genetic causes in 127 out of 174 (74%) probands that consisted in 6q24 abnormalities (n = 40), mutation in *KCNJ11* (n = 43), *ABCC8* (n = 31) or *INS* (n = 13). The most severe K_{ATP} channel mutations have been associated with neurological disorders. We performed refined neuropsychological and psychomotor investigations in 27 probands tested normal in a standard neurological examination. We evidenced, at variance with published data, Developmental Coordination Disorder (particularly visual-spatial dyspraxia) or attention deficits in all. We reported specific features of 6q24 genetic subtype as compared to K_{ATP} subtype: developmental defects involving the heart, kidneys or urinary tract (22% vs. 3%, $p = 0.002$), intra uterine growth retardation (92% vs. 48%, $p < 0.001$), and early age at diagnosis (median 5 days [1–120] vs. 45 5 days [1–278], $p < 0.001$). Remission of NDM occurred in 89 (51%) probands at a median age of 17 weeks. Recurrence probability was high, without difference between the 6q24 and the K_{ATP} channel probands (82% vs. 86%, $p = 0.36$, respectively).
Conclusion: Age at onset, birth weight or associated features can guide NDM genetic testing. This disease is frequently associated with neuropsychological and developmental defects specific to a genetic subtype and deserves specific multidisciplinary assessment.

What is the cause of cerebral edema in diabetic ketoacidosis?

INV9
What is the cause of cerebral edema in diabetic ketoacidosis? Is cerebral edema caused by cellular or vasogenic edema?

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Cerebral edema implies an excess accumulation of water in the brain which may be present in either the intracellular or extracellular compartments, or both. In the medical literature two types of cerebral edema have been reported in diabetic ketoacidosis, i.e., vasogenic and cytotoxic.

Types of cerebral edema: Vasogenic edema occurs when there is breakdown of the tight endothelial junctions that form the blood–brain-barrier, or when there is excess cerebral perfusion or hypoalbuminemia, or some combination of all of these factors. In vasogenic edema there is an influx of water from the vascular compartment into the extracellular and interstitial spaces. In cellular or cytotoxic edema the blood–brain-barrier is intact. The accumulation of water occurs within cells that swell because of bioenergetic failure leading to breakdown in cell membrane water and sodium homeostasis.

Brain imaging of water diffusion: Random motion of water molecules in homogeneous fluid-containing structures is relatively free and called isotropic diffusion. In the brain parenchyma, water motion is restricted by the presence of cellular structures that provide barriers to free diffusion, and this type of water diffusion is called anisotropic. In diffusion-weighted magnetic resonance imaging brain images can be generated that are dependent on water diffusion. A diffusion coefficient called the *apparent diffusion coefficient* (ADC) value can be calculated within each image voxel, and ADC maps can be produced. Since diffusion coefficients are high in fluids where diffusion is free, low signal is observed on diffusion imaging at $b = 1000$ mm^2/s (high signal on corresponding ADC maps). Normal cerebrospinal fluid is an example of this. In the presence of vasogenic edema high signal is seen on the ADC map, but lower than cerebrospinal fluid. On the other hand, if mobility of water molecules is restricted such as in cytotoxic edema high signal is observed on diffusion imaging at $b = 1000$ mm^2/s (low signal on corresponding ADC maps). Analysis of ADC histograms of the whole intracranial contents in the normal brain shows that there age developmental changes. For example, between the ages of 2 and 20 years peak ADC (i.e., highest frequency of pixel data) decreases exponentially from 900 to $\sim 600 \times 10^{-6}$ mm^2/s; between 20 and 60 years peak ADC is stable. This developmental change has significant consequence on using this parameter in both mechanistic and intervention studies.

Studies of ADC in diabetic ketoacidosis: To date, there have been a few small pediatric series that studied ADC maps during the acute phase of diabetic ketoacidosis. All of the authors conclude that their findings are consistent with vasogenic rather than cytotoxic edema. That is, within the first 72 hours ADC, if it changes, is increased rather than decreased. In keeping with these findings there is also evidence of increased cerebral blood flow and increased blood–brain-barrier permeability.

INV10
How can cerebral edema during treatment of DKA be avoided

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Currently it is unclear how CE can be avoided entirely in DKA. Clinical studies have not demonstrated any consistent risk factors but have been hampered by the rarity of the condition. However, although rare, it can be very serious, with significant morbidity and mortality, so the desire to avoid the condition has driven DKA guidelines for the past 2 decades. The implications for management guidelines of the various theories of the development of CE at the brain level discussed in the previous talk will be reviewed. The talk will discuss aspects of treatment of DKA which have been implicated in the development of CE, and how these could be modified to be safer, in particular, the contribution of insulin, sodium and fluids.

Many of the risk factors are related to the way in which the child presents with DKA and are therefore unmodifiable once DKA has supervened. Therefore avoidance of DKA completely at the diagnosis of type 1 diabetes is a laudable aim and would avoid much of the CE, which is more common at initial presentation of diabetes. Therefore various projects of public and professional education to prevent DKA will also be discussed.

INV11
Do the guidelines need to be changed?

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Each year, 65 000 children are diagnosed with type 1 diabetes (T1D) worldwide, and the frequency of diabetic ketoacidosis (DKA) at diagnosis varies from 12.8% to 80%. Different levels of disease awareness and healthcare provision partially explain the large variation. Only a few countries or centers have reported a significant decrease in DKA rates at diagnosis. DKA frequency in established diabetes remains unacceptably high. In the USA, at time of enrollment in the Type 1 Diabetes Exchange Registry, 9.9% patients 2 to <26 years reported ≥1 episode of DKA requiring hospitalization in the prior 12 months. Point-of-care measurement of blood β-hydroxybutyrate concentrations is useful for identifying patients at risk for DKA at home, for confirmation of diagnosis (≥3 mmol/L) and monitoring therapy, and should be included in DKA management guidelines.

The optimal protocol for treatment of DKA, especially rate and electrolyte composition of fluids and initial insulin dose, is still controversial. Regimens are based on physiologic principles and expert opinion. A literature search for publications on DKA from 2003 (since ESPE/LWPES consensus conference) performed in PubMed yielded 537 articles. Large single center series have reported excellent outcomes and a low incidence of significant cerebral edema using a physiologic approach based on principles of rehydration of hypertonic states together with meticulous clinical and biochemical monitoring. The multicenter PECARN FLUID study in the USA is the first large prospective RCT to evaluate fluid regimens for pediatric DKA; results are expected in 2016. Observational studies of another controversial topic; viz, the initial dose of insulin, 0.1 U vs. 0.05 U per kg per hour, are limited by lack of randomization of treatment protocols. Their findings, therefore, must be interpreted with caution. In the decade since the consensus conference, new data from prospective randomized trials in pediatric DKA are almost nonexistent.

Therapies for beta cell replacement on the horizon

INV12
Bringing mesenchymal stem cells into the clinic

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Mesenchymal Stromal Cells (MSCs) are non-hematopoietic progenitor cells that have immune-modulatory properties and promote peripheral tolerance. MSCs suppress alloreactive donor anti-host T-cell responses. Based on the immunomodulatory properties of MSCs along with the cells' ability to promote repair of injured tissue, it was hypothesized that MSCs may be beneficial in reversing inflammation. To date, MSCs have been infused intravenously to several hundred patients. No acute infusional toxicity has been reported.

Many questions remain to be answered to optimize MSC treatment. As MSCs are poor stimulators of alloresponses, the majority of patients have received MSCs derived from third-party mismatched donors. However, if and to what degree HLA-matching influences response in humans remains unclear. Furthermore, it is well established that MSC are rare cells *in vivo* and that culture *ex vivo* is necessary to obtain a sufficient number of cells for a therapeutic effect. The influence of culture conditions and media supplements on the efficacy of the cells needs to be established in clinical trials. This is particularly true since no efficacy marker has been established that predicts the clinical outcome of patients treated with MSCs. For example, measurements of MSC-induced lymphocyte suppression in mixed lymphocyte culture does not correlate with clinical response. Trials have used MSCs expanded in the presence of either fetal calf serum or platelet lysate. In vitro properties of MSC expanded in the two media are comparable, but undetected differences may still influence patient responses.

Response rates of MSC-treated patients with graft-versus-host disease and various automimmune disorders indicate that MSCs are a promising treatment tool. However, optimal cell expansion and donor selection will need to be evaluated in clinical trials.

INV13
Autologous islet transplantation – proof of principle without autoimmunity

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Autologous islet transplants have been performed for over 30 years in patients undergoing total pancreatectomy (TP) for management of chronic pancreatitis. In this procedure, the patient's pancreas is completely removed, mechanically and enzymatically digested with collagenase, and the islets are isolated and infused into the portal vein. While the procedure is nearly identical to islet allotransplants performed for treatment of labile type 1 diabetes, unlike allografts, islet autotransplants (IAT) are not subject to alloimmune rejection, autoimmune recurrence, or toxicity from immunosuppressive drugs. At the University of Minnesota, we have performed more than 500 IATs in patients with chronic pancreatitis. Over one-third of patients exhibit insulin independence at some time, and 90% have islet graft function (C-peptide positive) after the procedure. In some recipients, insulin independence has been sustained for over a decade. The likelihood of insulin independence varies with islet mass transplanted: At 1 year after IAT, 55% of patients with >5000 islet equivalents per kilogram body weight (IEQ/kg) are insulin independent, compared to 23% of those with 2500–5000 IEQ/kg, and 13% of those with <2500 IEQ/kg. 100% of those with >5000 IEQ/kg and 97% of those with >2500 IEQ/kg are C-peptide positive (stimulated value ≥0.6 ng/mL). Young children (<12 years old) have higher rates of insulin independence and longer durations of islet survival compared to adult IAT recipients. Compared to islet allografts for type 1 diabetes, islet autografts permit similar glycemic control and similar acute insulin response to glucose and arginine despite approximately half the islet mass of an allograft recipient.

These findings paint an optimistic future for islet transplantation for diabetes. Insulin independence can be achieved with a reasonably low islet mass transplanted when autoimmunity and alloimmunity are absent (or appropriately controlled).

New treatments for type 1 diabetes

INV14
C-peptide and microvascular complications of diabetes – Therapeutic possibilities

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Much new information on C-peptide physiology has appeared during the past 20 years. It has been shown that C-peptide binds specifically to cell membranes, elicits intracellular signaling via a G-protein and Ca^{2+}-dependent pathways, resulting in activation and increased expression of endothelial nitric oxide, Na^{+}, K^{+}-ATPase and several transcription factors of importance for anti-inflammatory and cell protective reactions. Recent evidence demonstrates that C-peptide deficiency may be an important contributing pathogenetic factor in the development of microvascular complications of type 1 diabetes. Intensive insulin therapy is known to retard but not prevent the development of complications. Studies in animal models of diabetes and early clinical trials in patients with type 1 diabetes demonstrate that C-peptide in replacement doses elicits beneficial effects on early stages of diabetes-induced functional and structural abnormalities of the peripheral nerves, the autonomic nervous system and the kidneys. Thus, clinical studies show that C-peptide replacement for 3–6 months can significantly improve the nerve conduction velocity of the sural nerve and lower the threshold for vibration perception. Moreover, C-peptide therapy for 3 months can diminish urinary albumin excretion by 40% in type 1 diabetes patients with microalbuminuria and unchanged glycemic control and blood pressure. There is still much to be learned about C-peptide and its mechanism of action but the available evidence presents the picture of an endogenous bioactive peptide with previously unrecognized therapeutic potential.

INV15
Faster and slower insulins

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During the last two decades, advances in diabetes technology have helped to improved patients daily life conditions. The introduction of short and long acting insulin analogs, has brought an increasing flexibility into life of the affected patients. Modern insulin pump treatment in combination with continuous glucose monitoring has further helped to normalize daily life conditions. Causal treatment approaches (vaccination techniques, islet cell transplantation, and artificial pancreas) are currently subject of intensive research efforts. Next to insulin glargine and insulin detemir, a new ultra-long acting insulin analog (insulin degludec) has been approved, which has demonstrated to reduce hypoglycemic events and enhance treatment flexibility. Ultra-short acting insulin formulations are expected to further improve prandial therapy. Simple treatment support approaches however may also have an unexpected beneficial impact on patients well being. Recently, a new medical device using a well known but yet unused physical phenomenon has been introduced for insulin therapy. After prandial s.c. insulin injection, the InsuPad device applies a defined warming and cooling cycle protocol, which enhances microvascular blood flow, resulting in accelerated insulin absorption and substantially lower insulin requirements. Pilot studies s well as a comprehensive real-world study have given evidence that HbA1c treatment targets can be achieved with ~30% lower insulin doses and a ~50% lower risk of hypoglycemic events in comparison to a control group not using the device. An insulin infusion system using a similar technology (InsuPatch) has been investigated in pediatric patients with comparable results. Further studies are currently on their way to confirm these encouraging results. In summary, intensive ongoing research efforts are constantly resulting in new drugs and products that help to reduce the disease-induced burden for children and adults suffering from type 1 diabetes.

INV16
GLP-1, DPP-IV inhibitors and Metformin

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Objectives and methods: Type 1 diabetes is characterized by loss of β-cell insulin secretion. There is also dysfunctional α-cell glucagon secretion and both factors result in abnormal glucose homeostasis. The mainstay of therapy to date has been centered on correcting the insulin deficiency as good glycemic control has been shown to improve microvascular and possibly macrovascular outcomes. Despite advances in insulin types and delivery systems the vast majority of individuals with type 1 diabetes fail to achieve recommended international glycemic targets. This is mainly due to problems with systemic hyperinsulinaemia, resulting in hypoglycemia and possible increased vascular risk, or hyperglucagonaemia which contributes to postprandial hyperglycemia.

The objectives are to review the existing literature and highlight mechanistically how non-insulin based therapies such as Metformin, glucagon-like peptitde-1 agonists and dipeptidyl peptidase-4 inhibitors may be used to treat type 1 diabetes.

Results: There is increasing interest in agents, which to date have been used to treat type 2 diabetes, as adjuncts to insulin therapy to improve glucose homeostasis. Metformin acts to inhibit hepatic glucose production and may afford cardioprotective benefits. Ongoing studies aim to establish if this is indeed the case. There is also an increasing evidence base that manipulating the incretin system with GLP-1 agonists and DPP-4 inhibitors may limit postprandial hyperglycemia, glycemic variability and weight gain with an overall reduction in HbA1c.

Conclusion: A significant proportion of individuals have sub-optimal glycemic control despite advances in insulin technology and delivery. Non-insulin-based adjuncts may help correct the pathophysiological disruption in glucose homeostasis seen in type 1 diabetes. Further studies are required to establish if this offers additional benefits over and above intensification of insulin therapy.

Can person-centered care improve metabolic control and quality of life?

INV17
Improving diabetes care for minority group adolescents – a stance in perceptions, attitudes, communication and context

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Prevention of health complications in children with diabetes type 1 requires demanding self-care. Teenagers belonging to an underprivileged ethnic minority are often least successful. Adolescents with diabetes need support from people around them, and care-giving organizations are important. A premise of person centered care (PCC) is that people have different views on their medical conditions and assess their situation from a rich context of personal history and social surroundings. Effective support to adolescents with diabetes demands that the care team is able to establish a dialogue with each young person that is well adjusted to their conceptions, attitudes and context. This study, in two pediatric diabetes clinics in Western Sweden, aims at extracting and providing such knowledge to improve the organization and performance of pediatric diabetes care teams.

WP1. Interviews with adolescents with diabetes 1 and a non-Swedish background, regarding their disease, self-care, social situation, and the care and support from the care giving organizations.

WP2. Study of diabetes care meetings to acquire knowledge of communication with these patients, aged 13–17, and to relate this knowledge to the concept of PCC.

WP3. Interviews with the care team professionals to describe and analyze their perceptions and practices regarding children with diabetes 1, as well as the rationale of the actual organization of care, as implemented in, e.g., care meetings.

WP4 Study of clinical consultations with adolescents regarding what type of shared decision making and how patient narratives are used in PCC regarding the planning of the care, and to what extent ethical or other problems arise due to this.

WP5. Design, implement and evaluate interventions to develop the organization of adolescent diabetes care in order to better adjust to identified needs, and support improved strategies with regard to communication and interaction with patients to strengthen their self-care ability.

INV18
UK: communication in patient-centered care

J.W. Gregory

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Providing patient-centered care is widely regarded as a key principle of high quality clinical services for young people with diabetes. Adherence issues are a major contribution to adverse outcomes for young people with diabetes. Skilled discussions with patients and their families from diagnosis to transition build on high quality, structured education, using age-appropriate information to assist the child's decision making. The principles of patient-centered communication and related techniques such as Motivational Interviewing (MI) which focus on helping people talk about and resolving their ambivalence about behavior change are important components of skilled communication by health-care staff working in pediatric diabetes services. MI is a method which is being increasingly used by a wide range of practitioners and can be particularly useful to those who are working with patients living with a long-term condition when ambivalence about behavior change is often a significant part of routine consultations.

In this presentation, the principles of high quality communication with patients to support patient-centered care will be reviewed. An overview will be provided of 7 recent UK-based studies which have evaluated optimal methods for delivering patient-centered care with highlights of results where available.

INV19
Can person-centered care improve metabolic control and quality of life?

D.G. Marrero

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Despite significant advances in therapy, many people with diabetes have less than optimal metabolic control, and continue to suffer from preventable complications. This reflects the interplay between the individual and the context in which he/she behaves is commonly cited in discussions of personal health choices and health and social policies. These perspectives have shifted in important ways over the past few decades. It was initially thought that simply providing information would change health care and health behaviors; all that was necessary to change clinical practice was to inform doctors of the reasons or research behind recommendations, and that changing individual health behavior was a simple matter of explaining the importance of performing specific actions. In the later decades of the 20th century, this view of clinicians and patients as obedient adopters of facts and recommendations was replaced by two somewhat divergent viewpoints – those emphasizing characteristics of the individual vs. those emphasizing the role of the broader contexts of economics, communities, organizations, cultures, and policies. This presentation will examine each of these in turn, before considering the synthesis of individual and context in a 21st century perspective of multilevel, multichannel influences. This consideration will include implications and lessons for clinical practice and development of improved approaches to promoting engagement in diabetes care, effective diabetes self-management, and quality of life among those with the disease.

Most girls will become mothers – Issues in different types of diabetes?

INV20

Maternal and perinatal outcome in pregnancies complicated by type 1 diabetes. Can we do any better?

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Based on national data from the Swedish Medical Birth Registry from 1991 to 2007 we investigated obstetric and perinatal outcomes in pregnancies complicated by type 1 diabetes (T1DM).

In 5089 type 1 diabetic pregnancies and 1.2 million controls we found significantly increased risks of all adverse outcomes in women with T1DM: adjusted odds ratios: severe preeclampsia: 4.47 (3.77–5.31), Caesarean delivery: 5.31 (4.97–5.69), stillbirth: 3.34 (2.46–4.55), perinatal mortality: 3.29 (2.50–4.33), major malformations: 2.50 (2.13–2.94) and large for gestational age: LGA (birth weight > +2 SD): 11.45 (10.61–12.36).

The high incidence of LGA inspired us to further characterize infant birth size. The distributions of BW, BL and HC were all unimodal but significantly shifted to the right of the normal reference. 47% were LGA with a BW >90th adjusted percentile, 46% of LGA infants were overweight at birth. A novel and unexpected finding was that fetal macrosomia was more pronounced in preterm and female infants. Surprisingly, neonatal outcome was independent of neonatal overweight in appropriate for gestational age (AGA) and LGA infants. However, the risk of adverse outcome was significantly increased in LGA compared with AGA infants born at term.

Maternal overweight/obesity was associated with even higher risks of adverse outcome in both women with and without T1DM. Within the T1DM cohort, obesity was associated with increased odds of major malformations adjusted OR: 1.77 (1.18–2.65) and preeclampsia adjusted OR: 1.74 (1.35–2.25).

Conclusion: In spite of major improvements in the management of type 1 diabetic pregnancies over the years, the present findings clearly demonstrate that T1DM pregnancies still are associated with significantly increased risk of adverse outcomes. An important observation is the rising incidence of LGA infants, which partly can be attributed to a concomitant increase in maternal BMI.

INV21

Which contraceptives should we recommend for our adolescents with diabetes?

E. Codner

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Routine care of the adolescent with type 1 diabetes (T1D) should include education about the risks of an unplanned pregnancy. The International Society of Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA) recommend that education regarding pregnancy prevention and planning should begin before menarche. Despite these recommendations, several studies have shown that adolescents with T1D are not aware of the risks of unplanned pregnancy and do not properly prevent this condition while engaging in risky behavior, especially during the late teen years.

The choice of a contraceptive method for women with T1D depends on the preferences and competencies of the patient, religious choices, duration of diabetes, the presence of complications, associated diseases and risky behaviors, and even public politics. In 2009, the WHO published new medical eligibility criteria for contraceptive use. In general, adolescents with diabetes duration of less than 20 years without vascular complications are eligible to use any method of contraception.

This talk will review the types of hormonal contraceptives available, including oral and injectable, the studies that have evaluated contraception in women with T1D and the current state of the art of side effects, including possible thrombosis associated with the new progestins (Fondecyt 1100123).

The Scylla and Charybdis of brain function; between hyper- and hypoglycemia

INV22
The impact of glycemic extremes on the developing brain: neuroimaging evidence

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In children with type 1 diabetes, as in adults, extreme fluctuations in blood glucose levels can produce acute neurological symptoms such as confusion, seizures, and altered consciousness. Long-term functional (cognitive) consequences, albeit subtle, have been noted by many studies, and may be particularly likely in children. Given the dynamic changes in the structure, function and metabolic demand of the brain during childhood, it has been hypothesized that glycemic extremes could alter normal developmental trajectories depending on the age at which these extremes are experienced. With the advent of neuroimaging techniques amenable for studying children, researchers have attempted to test this hypothesis and determine the neuropathophysiology underlying any long-term changes in cognitive function in vivo in humans. This talk will review evidence addressing the theory that severe hypoglycemia, chronic hyperglycemia and diabetic ketoacidosis have unique and measurable long-term impact on the developing brain. In addition, the strengths and weaknesses of different neuroimaging techniques, the need for a mechanistic understanding of any effects and the unanswered questions in this field will be discussed.

INV23
What causes neurocognitive dysfunction in children with diabetes: recurrent hypoglycemia, chronic hyperglycemia, or ???

C. Ryan

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Children with diabetes have an increased risk of cognitive dysfunction, with these effects being most pronounced in those who develop the disease in the first 5 to 7 years of life. Early research attributed these effects to recurrent episodes of moderately severe hypoglycemia. More recent studies have implicated a long history of poor metabolic control as the primary risk factor. In this presentation I question both views, and argue that at least in children, brain dysfunction does not develop gradually over an extended period of time, but rather, is the result of a relatively static 'lesion' that occurs primarily around the time around diagnosis, and which may affect some children to a far greater degree than others. Metabolic 'triggers', which may transiently affect the integrity of the blood–brain-barrier, include very high blood glucose values during the peri-onset period, as well as the metabolic changes associated with diabetic ketoacidosis. Following a brief summary of recent neurocognitive studies, I elaborate this 'early events' model, and describe supporting data from clinical and non-clinical research. Unlike other theoretical frameworks, this model can explain why cognitive dysfunction is apparent within 1–2 years of diagnosis, why there is not a continuing, progressive deterioration in cognition over time, and why the degree of cognitive dysfunction varies to such an extent within groups of children (and adults) with diabetes.

INV24
The highs and lows of metabolic stress in type 1 diabetes: clinical and psychological considerations

R.J. McCrimmon

Cardiovascular and Diabetes Medicine, University of Dundee, Dundee, UK

Research on adults with type 1 diabetes points to a relatively specific impact of this disease on a subset of cognitive domains, including intelligence, attention, psychomotor speed, cognitive flexibility, and visual perception. Early reports suggested that cognitive dysfunction in type 1 diabetes may be more pronounced in individuals exposed to repeated severe hypoglycemia, a finding consistent with anecdotal case reports of severe hypoglycemia. However, more recent longitudinal epidemiological studies have tended to implicate chronic hyperglycemia and microvascular disease in the pathogenesis of diabetes-related cognitive dysfunction. Despite this controversy, it is clear that there is increasing evidence that significant organic brain disease can occur in type 1 diabetes. The etiology is complex and likely to involve multiple risk factors; most notably the effects of chronic hyperglycemia and intermittent hypoglycemia. In this talk, I will review the current basic science literature, which suggests that the interaction between chronic hyperglycemia and recurrent hypoglycemia is a particularly toxic mix and one clinicians and their patients should strive to avoid.

Nutrition and carbohydrate counting: What should be included?

INV25
Carbohydrate counting and glycemic control in youth with type 1 diabetes: is counting carbohydrates sufficient

H.M. Quinn

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Dietary intake of carbohydrates has a major impact on glycemic control for persons with type 1 Diabetes (T1D) as this macronutrient has the greatest influence upon glycemic excursions. Managing carbohydrate intake, in an effort to optimize glycemic control, has long been the basis of medical nutrition therapy (MNT) for T1D. In the context of the DCCT study (Delahanty LM. et al Diabetes Care 1993), it has been shown that with accurate carbohydrate counting, optimal glycemic control can be achieved. With the availability of rapid acting insulin analogs, diet intake has been liberalized to accommodate varying schedules and appetites. Many patients have transitioned to physiologic insulin replacement using analog insulins in either basal bolus insulin regimens or pump therapy. These insulin programs add flexibility to lifestyles as well as meal planning but place greater emphasis on a proper understanding of diet, in particular carbohydrates, in order to calculate insulin doses. While carbohydrates have the largest influence on glycemic excursions, we know that fat and protein can contribute to these as well. Recent nutrition studies (Pankowska E. et al Diabetes Technology and Therapeutics 2011; Kordonouri O. et al Ped Diabetes 2012; Wolpert H. Diabetes Care April 2013) have shown that estimating insulin requirements to cover fat and protein components of the meal can help limit glycemic postprandial glucose excursions and improve glycemic control. However, asking patients to count grams or units of protein and fat intake in addition to carbohydrates will likely be difficult as many patients are already challenged with carbohydrate counting. Recent studies confirm that adolescents with T1D do not accurately count carbs (Diabetes Spectrum 2009). Since carbohydrates have the greatest impact on glycemic excursions, efforts to improve carbohydrate counting should be the primary emphasis in our collective efforts to improve glycemic control in youth with T1D.

INV26
Do fat and protein need insulin? The complex food counting in meal-bolus calculation

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Functional intensive insulin treatment (FIT) has become the most physiological method in managing children and adolescent with type 1 diabetes (T1D). Due to advances technology such as a personal insulin pump, respecting personal needs and an individual diet without glucose control deterioration become realistic. Continuous insulin applying trough different meal boluses allows to adopt insulin dose for mixt meal, with differ carb, fat and protein contains. But we observe the gap between the physiological insulin secretion and the most common model of insulin adjusting in FIT. I want to argue that also fat and protein contains in meal should be considered in programming prandial insulin dose. What we know about a factors influencing postprandial hyperglycemia in longer than 2 hours after a meal will be present. We also ask what are the evidences of the effectiveness of using different boluses for meal. We present original concept of prandial insulin calculation. According to this concept all meal components, which are sources of energy are taken into account in insulin programming. In this new algorithm, called as the Warsaw Pump Therapy School (WPTS) formula, the insulin dose is calculated for the carbohydrate amount of the meal, and is to be delivered immediately as a quick bolus, and for the fat and protein amount to be delivered in a modified extended bolus. The effectiveness, patients' adherence as well the reality of using this algorithm in diabetes practices are a great challenge. Nutrition process and insulin programming combine into one meter is critical for children and adolescent with T1D. Therefore want to invite for discussion on this issue.

INV27
How do we get teenagers interested in bolus calculations?

D. Cavan

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In order to effectively manage their diabetes, whether using an insulin pump or multiple injections, teenagers are requires to give regular bolus doses prior to meals and to correct hyperglycemia. In order to give the correct dose, they need to have an understanding about the carbohydrate content of meals and the physiological and lifestyle factors which affect insulin requirements. They also need to know their current glucose level, their own insulin dosing parameters (such as insulin to carbohydrate ratio and sensitivity factor), and to be able to perform complex mathematics to calculate the dose. Finally, they need to prioritize their diabetes management to ensure that attention to these details is part of their daily routine.

Many teenagers with diabetes, however, are more interested in getting on with their life, than in the detail of intensive insulin treatment. Many have difficulty with one or more of these requirements and as a result may guess or even omit bolus doses, and/or omit blood glucose testing. So, even before addressing how we get teenagers interested in bolus calculations, there is often a need to explore the barriers to giving bolus insulin or to performing blood tests. Barriers such as difficulty with mathematics can be overcome by using blood glucose meters which have a bolus advisor. Problems with calculating carbohydrate content can be overcome by tools such as smartphone apps. Soemtimes effective use of such tools can in itself help overcome barriers to blood testing. And only then is it likely that the individual will be willing to explore the potential benefits of bolus calculations, such as better glucose control, less hypoglycemia, better performance at sport or at school, or the ability to eat freely.

Pancreas cross-talks with other organs

INV28
The liver – beta-cell circuit

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Insulin secreted by the pancreatic β-cells passes directly into the portal circulation and 50% is extracted with each pass through the liver. Thus portal insulin concentrations are greater than those observed in the peripheral circulation. Portal insulin extraction is closely related to hepatic insulin sensitivity, and resistance is associated with increased peripheral insulin concentrations. Impaired β-cell function or late peaking of insulin after a meal will result in failure to suppress hepatic glucose production as well as reduced peripheral glucose uptake. This can lead to impaired glucose tolerance, an early stage along the road to type 2 diabetes (T2D). Studies of healthy subjects, selected on the basis of common genotypes associated with extremes of insulin secretion and thus an unbiased reflection of insulin secretory capacity, will be presented demonstrating effects on hepatic lipid metabolism, as well as circulating IGF-1 concentrations which could relate to T2D risk.

Cross-talk between the pancreatic β-cell and the liver is also critical to metabolic control in patients with type 1 diabetes (T1D). Preservation of C-peptide positivity improves glycemic control and, as demonstrated by the DCCT, may reduce the risk for long-term microvascular complications. Portal insulin concentrations are critical for the regulation of the hepatic growth hormone (GH) receptor and thus hepatic IGF-1 generation. Patients with T1D who become C-peptide negative have low circulating IGF-1 concentrations and reduced IGF-1 bioactivity, which lead to feedback drive for greater GH secretion. These abnormalities have been implicated in the development of the insulin resistance observed in T1D and subsequent risk for microvascular complications. Normalization of the GH/ IGF-1 axis is rarely achieved with continuous subcutaneous insulin delivery in those who are C-peptide negative whereas portal insulin delivery is effective. With the drive to provide a more responsive physiological delivery of insulin with closed loop systems, a re-examination of methods for portal administration should be considered.

VIDIS Symposium: Viruses and diabetes: Candidates, targets, and mechanisms

INV29
Role of influenza viruses in the etiopathogenesis of diabetes

L. Piemonti

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The rapid worldwide incidence increase suggests a major role for environmental factors in the etiology of type 1 diabetes (T1D). According to cross-sectional and prospective studies on T1D patients and/or prediabetic individuals, virus infections may be one of these. Recently, in humans there have been reports of pancreatic damage associated to H1N1pdm influenza A virus infection, including both acute pancreatitis and onset of T1D. To date there has been no attempt to establish whether influenza viruses are able to grow in pancreatic cells in vitro and no data are available on consequences of influenza virus replication in the pancreas in vivo. In this study we explored the implications of influenza infection on pancreatic endocrine function in animal model, and we performed in vitro experiments aiming to establish the occurrence, extent and implications of influenza A virus infection in human cells of pancreatic origin. For the in vivo studies we selected the turkey as a model, due to the fact that turkeys are highly susceptible to influenza infection and pancreatic damage is often observed as a postmortem lesion. For the in vitro studies we selected both established human pancreatic cell lines (including human insulinoma and pancreatic duct cell lines) and primary culture of human pancreatic islets. Our results suggest that in vitro human influenza A viruses are able to grow in human pancreatic primary cells and cell lines. On the other hand, in vivo influenza A viruses are able to colonize the pancreas of experimentally infected poults and cause metabolic consequences reflecting endocrine and exocrine damage.

INV30
Enterovirus infection in the pancreas

S.J. Richardson

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An increasing body of circumstantial evidence has implicated enteroviral infection of islet beta-cells as an important factor in the etiology of human type 1 diabetes. Researchers from two large collaborative networks, PEVNET and nPOD-V, are using a wide range of complementary methodologies to examine pancreatic tissue from individuals with type 1 diabetes (UK, nPOD) or who are islet autoantibody positive (nPOD) for the presence of an enteroviral infection of islet beta cells. The studies suggest that in diabetes, such infections do not follow the typical course in which phases of large scale viral replication lead to extensive cell lysis. Instead, they appear to exist in a latent (more persistent) form in which viral replication occurs only very slowly but where the presence of the viral genome promotes subtle changes in islet cell physiology These may ultimately culminate in the development of islet autoimmunity.

Long-term diabetes complications

INV31
Long-term diabetes complications – the global perspective – situation and resource availability

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It is well established that microvascular and macrovascular complications occur earlier and more commonly when blood glucose control is suboptimal. Thus emphasis must always be placed on improving control. Advances in insulin delivery, blood glucose monitoring, education, and partial self-management have lowered average HbA1c over the decades, reducing the incidence of serious complications and increasing life expectancy. Further improvement will hopefully come as the 'loop' is closed, and complications are treated earlier and more effectively.

Screening and early intervention for complications is critical. ISPAD guidelines recommend annual screening for retinopathy and neuropathy from age 11 years (y) with 2y duration and from age 9y with 5y duration, annual blood pressure checks, and lipids measured every 5y after 11y of age. Neuropathy, growth and pubertal development are also monitored. It must be remembered that pediatric endocrinologists generally only look after the person for a relatively small part of their lifespan. Successful transition to adult services and quality ongoing care is crucial.

Unfortunately access to care varies markedly around the world, and in many developing countries average HbA1cs are very high, with serious complications sometimes evident in adolescents and young adults. Mauriac Syndrome is still not infrequently encountered. The International Diabetes Federation *Life for a Child* (LFAC) Program Index of Diabetes Care for Children and Youth has demonstrated stark contrasts in the provision of care between the developed world and most developing countries. This is evident in both access to supplies (insulin, meters and strips etc.) and complications screening (HbA1c, microalbuminuria and eye and foot screening). Fortunately the situation is starting to improve in some countries due to the dedicated efforts of local champions – health professionals and lay people – with the support of LFAC, ISPAD, and other international groups.

INV32
Cancer as a long term complication in T1DM and T2DM

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It is currently unclear if type 1 diabetes is associated with an increased risk of certain cancers. Although such associations have been reported for leukemia, thyroid and other endocrine cancers, these associations have been quite variable in the literature. At present, I think that the conclusion is that this is an area that has not been sufficiently carefully analyzed and the results are conjectural.

In contrast, type 2 diabetes is clearly associated with an increased risk of several cancers including in the pancreas, liver, colon, breast and endometrium. Furthermore, mortality in cancer is increased in patients with type 2 diabetes for unclear reasons. Less regular screening and/or less intensive therapy due to complications have been suggested as possible reasons.

There are several common risk factors for cancer in patients with type 2 diabetes such as older age and obesity. However, the increased risk remains even after statistical adjustments for these known factors. Recent interest has been focused on the potential role of therapy, insulin resistance per se with the associated hyperinsulinemia and elevated IGF levels. Metformin has frequently been shown to have a protective effect on cancer risk, possibly by activating AMPKinase and cell growth.

Insulin, like IGF, is a growth factor and can also cross-talk with IGF receptors in cancer cells. Experimental data suggest that insulin can increase growth of tumor cells but it is important to emphasize that insulin is NOT oncogenic by itself. Another therapy that has attracted increased attention is GLP-1 since it can increase the risk of pancreatitis and stimulate growth of non-endocrine cells in the pancreas. However, the potential association with an increased risk of pancreatic cancer is still conjectural.

Clinical outcomes from population-based diabetes registries

INV33
Scandinavian pediatric registries: NordicDiabKids

J. Svensson & NordicDiabKids

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Objectives: NordicDiabKids is collaboration initiated in 2008 between childhood diabetes registries from four Nordic countries. The collaboration was initiated with the aim to harmonize our indicators of quality of diabetes care as well as mutual inspiration for improving care in Nordic countries.
Methods: The basis of the registries is nationwide registration of all childhood cases with diabetes and clinical data allowing for updated analysis of incidence and prevalence of different types of diabetes as well as prospectively follow-up on quality of care.
Results: The establishment of the quality registries with the present organizations were 1996 for Denmark (D) and Iceland (I), 2000 and 2006 for Sweden (S) and Norway (N) respectively. Together the four countries cover a population of 20 million people. The four registries are comparable concerning the registration of clinical outcome factors and treatment data, with some differences. The measure of Hba1c is centralized in D, I and N, whereas in S they use the local measured value. The registration of data in N and D is annually; whereas I and S collect data at every visit. All four registries have national bench-marking and have been able to show improved results confirming the value of quality registers. Combining registries improve the power to study minority groups. In all the Nordic countries health care facilities are tax financed. Despite the equal access to health care, there are noticeably differences with the same tendency towards a worse metabolic outcome between non-Nordic children and Nordic children. The latter partly explained by less intensive treatment regimens. We also find younger age at onset and a different gender distribution in non-Nordic children indicating a common background for the observed differences.
Conclusions: Nationwide registries improve diabetes care; combining registries improve our ability to study smaller groups to detect differences – the first step to change for the better.

INV34
Do our pediatric patients get complications as young adults?

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Intensive treatment of patients with type 1 diabetes delays the onset of long-term complications.
Objectives: Based on information from two nation-wide quality registers, we investigated to which extent HbA1c values 3–15 months after diagnosis in childhood are related to metabolic control, albuminuria and retinopathy in early adulthood.
Methods: Every Swedish resident has a unique personal identity number. This makes it possible to link information from various population-based registers to individuals and follow these individuals over time. In Sweden, physicians register all children and adolescents with type 1 diabetes mellitus in the Swedish Pediatric Quality Registry. After 18 years of age, people with diabetes are followed by the Swedish National Diabetes Register. We identified 1543 children and adolescents with a mean age of 13.9 years at diagnosis and a mean duration of type 1 diabetes mellitus of 7.1 years.
Results: Children and adolescents with poor metabolic control (mean HbA1c $\geq$ 70 mmol/mol (8.6%)) adjacent to diagnosis had a significantly higher mean HbA1c value years later as adults than did patients with a good metabolic control (<50 mmol/mol (6.7%)($p < 0.001$)). The patients in the group with poor metabolic control were also less physically active and a higher percentage of were smoking as adults. The proportion of females was higher in the poor metabolic group. Patients with a high mean HbA1c 3–15 months after diagnosis had significantly more often macroalbuminuria and retinopathy in early adulthood.
Conclusions: Metabolic control adjacent to the diagnosis of type 1 diabetes in childhood or adolescence is linked to metabolic control in early adulthood. It is therefore very important that pediatric diabetes teams identify key factors for successful early metabolic control. Actively using quality registries may assist the teams in finding such key factors.

INV35
Lessons from Scotland

K.J. Robertson

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In 1983 the Scottish Study Group for the care of Diabetes in the Young was established and set up a register for patients under 15 years. This register has been validated using capture-recapture methodology and is highly regarded. It has been instrumental in studies of prevalence and incidence as well as cross-sectional assessment of clinical status. In a separate development, and via several iterations, adult diabetes services have been supported by an information technology platform (originally DARTS) which harnesses clinical information from secondary care, general practice and the national eye screening service. This comprehensive source has furnished data for the annual Scottish Diabetes Survey for almost 10 years. For the first time, this platform (now SCI-Diabetes) is being rolled out as an entirely web-based product to all pediatric services in Scotland. This presentation will describe the process, some of the pitfalls and early experiences of having a National Children´s Diabetes Services clinical database and suggest the sorts of outcomes that we can anticipate.

Successful initiatives in emerging countries: GPED symposium

INV36
Sudan: childhood diabetes teams

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Objectives: To see the impact of establishing childhood diabetes clinics staffed with multidisciplinary teams in Sudan.
Methods: The Sudanese Childhood Diabetes Association in collaboration with the World Diabetes Foundation and the Government established 30 clinics in all states of Sudan. National guidelines for management as well as health education materials were produced. Insulin was provided free. Meters were provided free to most children particularly the poor who formed the majority. Parents were educated. Some clinics have facilities for point of care HbA1c assay. Telecommunication facilities with mobile phones were provided. In parallel school health Program was established and teachers trained. Media were intensively used for improving public awareness.
Results: Almost 30 clinics including 2 tertiary care centers were established. The minimum number of each team was 2 (general pediatrician and an educator or dietician).The major problem faced here was movement and immigration. The main barrier to SBGM was the cost of strips. The percentage of children presenting with DKA at onset dropped significantly. and the mortality and morbidity have improved. Many of the previously known misconcepts about the disease and its management have disappeared. The mean HBA1c level varies from one center to another but is still suboptimal and needs more work. Cases are screened for chronic complications. Still relatively high numbers develop nephropathy early.
Conclusion: Childhood diabetes multidisciplinary staffed clinics are now accessible in all states of Sudan. Management guidelines are unified and available as well as insulin. Public and professionals awareness has improved markedly. The mean levels of HbA1c is still suboptimal. The morbidity and mortality from acute complications have shown marked improvement. Sustainability of these clinics is still a challenge that needs cooperation from various national and international bodies.

INV37
India: MDI in a poor population

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Background: 69 million Indians have DM, 10% are children. Poor children with T1DM either have no treatment or receive 2 doses of premixed insulin and minimal monitoring. Recurrent complications, including hypoglycemia and death are common.
Objective: Implement a Multiple Dose Injections (MDI) insulin treatment program in poor, limited education patient population.
Setting: Project site was a 150 bed charitable hospital in Haridwar, India with limited resources. Prior to 2006, no child with DM survived to adulthood. In 2006, a diabetes management program with MDI was introduced in 3 children. The program progressively expanded and, in 2012, 39 children were followed.
Methods: A team-based approach consisting of a physician, a diabetic educator and a social worker was used. All patients were treated with MDI using Glargine and Humalin-R insulin. Extensive patient education was provided that was culturally and linguistically appropriate and to the level of their literacy. Carbohydrate counting of Indian food was introduced with patients utilizing home glucose monitoring. A structured program including home visits, telephone support and group meetings was implemented.
Results: From 2006–2012, 39 patients (56% male) were followed with mean age was 15.1 years (range 7–23) and mean duration of DM was 3.6 years (range 5 months–16 years). Hb A1c was checked every 4 months. In 2012, mean value of HgbA1c was 8.53% (SD 1.65). No patient developed significant hypoglycemia, required hospital admission or missed school as a result of DM. Growth and development was age-appropriate.
Conclusion: A comprehensive team-based approach incorporating individualized patient education, environmental assessment and social support facilitates the safe and effective implementation of an MDI based diabetes management program. This program demonstrates that excellent clinical results without complications can be obtained in poor and uneducated patients, by providing structured support and necessary resources.

INV38
China: World Diabetes Foundation project on diabetes in children

X. Luo, WDF Project on Management of Diabetes in Children in China

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Although the reported incidence of type 1 diabetes (T1DM) in children was relatively low in China, the prevalence of T1DM cannot be underestimated with the large population. We aimed to establish pediatric diabetes centers to increase diagnosis rate and improve access to quality of care through training to HCPs, and to facilitate a survey to raise the awareness of pediatric diabetes and evaluate the diagnosis and treatment situation, and to improve the awareness and quality of care of the caregivers of the children with diabetes. Training-the-trainer (TTT) courses will be conducted and followed by training workshops for more HCPs. A minimum of 50 children with diabetes will be treated and managed in each center and all the caregivers will be educated. A survey will be conducted among the centers to investigate the status of diabetes care. Diabetes registration system will be established. Thirty two pediatric diabetes centers were established in 25 cities across China. Over 732 pediatric diabetes patients (T1DM 679, T2DM 45, uncertain 8) were enrolled and registered so far. Preliminary data showed the mean age of T1DM was 7.3 ± 3.7 years, with 213 (31.4%) under 5 and 466 (68.6%) over 5 years old. The overall frequency of diabetic ketoacidosis (DKA) was 353/679 (52%) in T1DM, with 105 (49.3%) under 5 and 248 (53.2%) over 5 years old. The incidence of severe hypoglycemia was 18.8% (141 cases) and was significantly higher among younger children. Of all the patients, the mean HbA1c level was 10.57 (T1DM 10.66 and T2DM 9.49). Among the T1DM, HbA1c levels were negative correlated with age, total family income and education level of parents. The HbA1c levels were also significantly correlated with the incidence of hypoglycemia, but not with the frequency of DKA. T1DM is still the major form of diabetes in children under 14 years old in China. The WDF initiatives were promising in emerging countries and more practical collaborations from international societies were expected.

Type 2 diabetes, twice as bad?

INV39

Is type 2 diabetes more dangerous than type 1 diabetes?

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Childhood obesity involves considerable associated morbidity. The metabolic aspects associated with obesity include altered glucose metabolism, dyslipidemia, non alcoholic fatty liver disease (NAFLD) and sub clinical degrees of inflammation. The temporal presentation of these biomarkers and medical conditions in relation to the development and progression of obesity is highly variable. While obesity is postulated to drive insulin resistance which accelerates the development of obesity related morbidity, in some children, insulin resistance may be present prior to the development of massive obesity. Similarly, NAFLD may be present early in the course of obesity development and drive the development of whole body insulin resistance. The patterns of lipid deposition in multiple depots and not necessarily the degree of total obesity are strongly associated with the metabolic phenotype of the obese child. It is still debatable whether the combination of insulin resistance and low grade inflammation is the driver of obesity related complications development or vice versa.

INV40

What are the drugs of choice in the teenager with type 2 diabetes?

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Since type 2 diabetes has only been identified as a disorder affecting adolescents relatively recently, pediatricians do not have an extensive body of evidence on which to base decisions regarding pharmacologic therapy of type 2 diabetes in this population. Thus, until recently, treatment has been based on extrapolation from findings in studies of adults with type 2 diabetes. However, it is becoming increasingly clear that type 2 diabetes in youth differs from type 2 diabetes in adults in important ways, including interactions with puberty, rapid deterioration in beta-cell function, and association with psychosocial challenges that place adherence at risk. Therefore, it is now clear that approaches to treatment of type 2 diabetes in youth will need to be specifically identified. This challenge is made more difficult by the small size of the population of youth with type 2 diabetes available for study, such that metformin remains the only oral agent approved for use. The recently completed TODAY Study provides comprehensive new insight about type 2 diabetes in youth, providing the evidence base for an initial approach to treatment, while pointing out the questions still remaining regarding treatment for those in whom glycemic control is lost. In this session, we will review the current state of knowledge regarding the action of anti-diabetes medications in youth, the guidance provided by the results of the TODAY study, the input of recent expert guidelines, and the status of clinical trials of new agents. An approach to selection of initial and subsequent agents for treatment of type 2 diabetes in youth will be provided.

Artificial pancreas projects; How far away is the closed loop? JDRF Symposium

INV41
DREAM Project (Germany, Israel, Slovenia)

M. Phillip, DREAM Consortium

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Maintenance of nocturnal euglycemia is extremely important and challenging, since most cases of severe hypoglycemic events occur at night, accounting for 75% of total hypoglycemic seizures in children, and might be associated with the 6% of deaths in patients with type 1 diabetes under age of 40 years. Despite the development made in the field of diabetes technology, a risk of hypoglycemia is still present in all current available therapies.

To address this challenge, the Diabetes wiREless Artificial Pancreas ConsortiuM (DREAM) was established aiming at reducing the risk of nocturnal hypoglycemia and improving nocturnal blood glucose control using the MD-Logic Artificial Pancreas. The MD-Logic is a wireless fully automated closed-loop system based on a fuzzy logic theory algorithm, a learning algorithm, a personalized system setting and alerts module. Since October 2010, we have conducted *in silico* studies using the FDA approved UVA simulator (N = 300 virtual patients) as well as 6 clinical studies which took place in Israel, Germany and Slovenia (N = 123 type 1 diabetes patients). The clinical studies included feasibility in hospital studies as well as prospective randomized controlled, multicenter multinational crossover studies conducted in three settings:

i in hospital,
ii at a diabetes camp and
iii 4-night study at patients´ homes.

Studies results demonstrated the safety and efficacy of using the MD-Logic Artificial Pancreas for overnight glucose control. In all studies, the MD-Logic artificial pancreas system achieved significantly less hypoglycemia and tighter overnight glucose control compared to standard treatment (i.e., CSII or sensor augmented pump therapy). The DREAM consortium is now evaluating the MD-Logic system in a longer study period at patients' homes.

INV42
Cambridge automated closed loop system (UK)

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The establishment of automated closed-loop (CL) insulin delivery systems, exploiting recent advances in glucose responsive insulin algorithm development and the use of modern subcutaneous insulin pump delivery and glucose sensing systems, is seen a key step towards realizing the goal of (near-normal) physiological insulin replacement therapy for patients with type 1 diabetes (T1D). The Artificial Pancreas in Cambridge (APCam) research programme has, since 2006, been developing a subcutaneous CL system aimed at the avoidance of nocturnal hypoglycemia and at improving glycemic control in children and adolescents with T1D. Employing an in-house developed 'model-predictive control' algorithm and using standard, commercially, available subcutaneous insulin pump and continuous glucose monitoring (CGM) devices, a series of randomized, controlled clinical studies have been completed that have focused on demonstrating the safety, efficacy and utility of our CL set-up ('Florence CL system') under different conditions (e.g., diet and exercise) and settings (manual and automated control). Testing in the clinical research facility has successfully demonstrated that CL therapy results in significant improvements in blood glucose control in young people (aged 5 to 18 years) with T1D, with reduction of risk of nocturnal hypoglycemia (BG < 3.9 mmol/L) and increased time with blood glucose values in target (BG 3.9 to 8.0 mmol/L) when compared to insulin pump therapy alone. The results of these studies will be reviewed together with data from a recently competed pilot study of unsupervised nocturnal automated CL application under 'real-life' conditions in the home setting.