KL1
Pathways in type 1 diabetes
J. A. Todd
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Life-long dependency on insulin injections owing to catastrophic failure of pancreatic b cells to secrete insulin (type 1 diabetes), appears, in many cases, to be due to a destruction of b cells by the body’s own immune system. From epidemiological, histological and genetic studies in humans we know that the incidence of type 1 diabetes is (a) increasing in frequency by 3% per year, (b) season-dependent, (c) characterised by a north-south gradient across Europe and (d) strongly inherited. The susceptibility genes discovered so far provide major clues to the nature of the diabetogenic autoimmune system: immune recognition of b-cell antigens, including insulin itself, by HLA class II genes; insulin gene expression in the T cell factory, the thymus; CTLA-4-regulated T cell expansion; phosphatase, PTPN22, -regulated T cell signalling thresholds; and the IL-2 cytokine receptor, CD25, involved in T regulatory or suppressor cell functions. Recent advances in technology and clinical resources are allowing the identification of new genes and pathway. The latest disease association results, the viral double-stranded RNA receptor, interferon-induced helicase, IFIH1, and the enzyme CYP27B1, which catalyses the final step in vitamin D production, may be pointing to interactions between common environmental factors and disease incidence.

KL2
Diabetic nephropathy
M. E. Cooper
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Diabetic nephropathy remains a major cause of morbidity and mortality in the type 1 diabetic population. Although the prognosis has clearly improved over the last 2 decades, probably as a result of better glycaemic control and early introduction of antihypertensive drugs such as agents which interrupt the renin-angiotensin system, diabetes continues to be the major cause of end-stage renal failure in the Western World. As the natural history of diabetic nephropathy has become increasingly elucidated, it has been generally appreciated that the early identification of microalbuminuric individuals has allowed clinicians to target these individuals at high risk of progression to more advanced renal disease with intensified glycaemic control and introduction of agents such as ACE inhibitors and AII receptor antagonists. However, these strategies often only delay rather than prevent diabetic nephropathy. Thus, much research is focussed on identifying mechanisms of diabetes related renal injury and developing new treatments to directly interrupt these pathophysiological pathways. This has led to drugs which inhibit accumulation of advanced glycated end products and inhibitors of intracellular signalling molecules such as PKC beta. Clinical studies are currently in progress to evaluate the role of these agents in the setting of concurrent ACE inhibitor or AII antagonist therapy. A major finding for ongoing follow up of the DCCT study (known as EDIC) has been the realisation that there is ‘hyperglycaemic memory,’ i.e. in subjects who previously had poor glycaemic control but subsequently improved their glucose levels, there continues to be evidence of ongoing progression of microvascular complications including nephropathy. This emphasises the critical role of achieving the best glucose control in children and adolescents with diabetes to avoid subsequent increased progression of renal complications in adulthood. Recent studies by our group have implicated epigenetic mechanisms and in particular glucose induced change is chromatin remodelling as a potential explanation for this phenomenon of ‘hyperglycaemic memory.’ It is hoped that by further delineating the molecular and cellular mechanisms implicated in diabetic complications, more rational strategies can be designed and implemented to prevent, treat and reverse diabetic complications including nephropathy. In the interim, even in subjects with no evidence of complications it remains critical to optimise metabolic control and to consider early introduction of antihypertensive agents in children and adolescents with type 1 diabetes. It is likely that the epidemic of type 2 diabetes which is now extending into paediatric endocrinology will also lead to increased numbers of children with type 2 diabetes being at risk of complications such as nephropathy.

KL3
Screening for type 2 diabetes
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A Consensus Panel convened by the American Diabetes Association in 2000 recommended that testing for type 2 diabetes be performed every 2 years in the context of a health care visit in overweight/obese youth ≥10 years of age children if any two of the following risk factors were present: Family history of type 2 diabetes in 1st or 2nd degree relatives; Race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander); Or Signs of insulin resistance or conditions associated with insulin resistance. The Panel recommended that screening be done with fasting plasma glucose. Assessment of the ADA recommendations: Review of recent studies screening for type 2 diabetes, including the STOPP-T2D trial. In multiple studies in overweight teens, many from high-risk ethnic groups or with a positive family history of diabetes, 0–6% have been found to have unrecognised diabetes on evaluation. This has been replicated in population-based diabetes screening. In a recent study in 1740 8th grade students (The STOPP-T2D Prevention Study Group) from high-risk racial/ethnic groups and with 49% with a BMI ≥85th percentile, 0.4% had fasting glucose ≥126 mg/dl and 0.1% ≥200 mg/dl. These data would suggest that screening asymptomatic - even high-risk - children and youth for type 2 diabetes is not indicated in the public health and medical arenas (despite the recommendation of the ADA Consensus Panel). However, there are data to suggest that screening for overweight/obesity in youth should occur. This will help determine who to refer for lifestyle counselling and early intervention to impact on obesity as a risk factor for diabetes.

S1
Sweet dreams? Finding genes for type 2 diabetes
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The substantial inherited component of type 2 diabetes (T2D) susceptibility means that important insights into disease pathogenesis can be obtained by susceptibility gene identification. Whilst there has been spectacular success in identifying genes responsible for monogenic forms of diabetes, characterisation of genes influencing ‘typical’ multifactorial T2D has proceeded more slowly; each individual susceptibility variant has only a modest effect on disease risk. Until recently, much of the effort to define such variants has been compromised by methodological limitations, of which inadequate sample size has been most important. Many existing claims of variants associated with T2D are probably spurious. These difficulties are increasingly surmountable. Several T2D-susceptibility genes have been identified through candidate gene and positional cloning approaches. For example, common variants in PPARG and KCNJ11 each predispose to T2D with odds ratios of ~1.2 across many studies in diverse populations. The consequences of variation within TCPTL2 on T2D risk seem
Invited Speakers

even greater. These examples emphasise the improving prospects for T2D gene identification. It is clear that: (a) large studies are required for robust identification of susceptibility variants; (b) examination of genes of interest needs to be exhaustive because unheralded functional variation may occur well outside coding regions; and (c) diabetogenes so far identified emphasise the relative importance of inherited effects on beta-cell function, rather than insulin action. A comprehensive view of the landscape of genetic susceptibility to T2D is within sight. By typing sufficient markers (many hundreds of thousands) in large enough sample sets (many thousands) we can expect to capture a high proportion of the variants with meaningful disease associations. A number of such genomewide association studies are underway, including our own involvement in the Wellcome Trust Case Control Consortium. As part of the WTCCC we are genotyping 2000 cases and 3000 controls for 500 000 SNPs genome wide. These studies present very significant informatics and analytical challenges and require novel high-throughput approaches to relate genetic association findings to relevant sources of functional and biological data. However, we can expect them to provide a wealth of insights into the inherited basis for T2D susceptibility.

S2

Severe insulin resistance syndromes

D. B. Savage

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Insulin resistance, which can be defined as a state of reduced responsiveness to normal circulating levels of insulin, plays a major role in the development of type 2 diabetes. Studies in mono-/oligogenic forms of extreme insulin resistance are important for three reasons: i) individuals with these disorders suffer significant morbidity and may benefit from targeted therapy; ii) insights obtained from such rare disorders frequently yield novel information regarding the biological functions of mutated proteins; iii) less deleterious genetic variants in proteins which when severely disrupted cause severe phenotypes may be involved in common forms of complex disease. Examples will be presented and discussed.

S3

Genetic syndromes and diabetes mellitus

T. G. Barrett

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Up until about 15 years ago, all childhood diabetes was considered to be type 1; no differential diagnosis was required for children presenting with osmotic symptoms; and diabetes was regarded as a practical management problem only. Recently, diabetes in association with extra-pancreatic features have been characterised as syndromes; the genetic bases identified, and diagnostic testing and specific treatments have become available. These syndromes are individually rare, but collectively account for a disproportionate amount of time and resources in diabetic clinics, and have major implications for family counselling. Many of these have aided our understanding of important pathways in normal insulin metabolism. Four syndromes demonstrate recent progress: Wolfram, Wolcott-Rollison, Rogers, and Alstrom syndromes. Wolfram syndrome is the association of diabetes and progressive optic atrophy. Children present with typical osmotic symptoms and insulin dependence but gradually progress to loss of vision, sensorineural deafness, diabetes insipidus and neurodegeneration. Mutations have been shown in WFS1, a gene encoding Wolframin, an endoplasmic reticulum protein. Wolframin is thought to be involved in endoplasmic reticulum stress, a cellular protective mechanism particularly important in secretory cells such as beta cells. Cells lacking Wolframin are unable to process and remove unfolded or misfolded proteins as part of the normal process reading cellular machinery; the result is cell death by apoptosis. Secondly, Wolcott-Rollison syndrome presents with neonatal onset diabetes and hepatic failure; patients also have a skeletal dysplasia and developmental delay. The causative gene, EIF2AK3, encodes another essential component of the endoplasmic reticulum stress response, the Eukaryotic Translation Initiation Factor 2-alpha kinase 3 (also called PERK). This enzyme phosphorylates EIF2A at Ser51 to regulate the synthesis of unfolded proteins in the endoplasmic reticulum (ER). Diabetes occurs as a result of accumulated unfolded proteins triggering beta cell apoptosis. Thirdly, Rogers syndrome presents with the triad of insulin dependent diabetes, sideroblastic anaemia and sensorineural deafness under 5 years of age. This monogenic syndrome is due to mutations in SLC19A2, encoding a thiamine transporter. Thiamine is an essential cofactor for several enzymatic processes involved in carbohydrate metabolism. Endogenous insulin secretion is increased by pharmacologic doses of thiamine, illuminating thiamine as essential for normal glucose and insulin metabolism and making this a novel vitamin dependent form of diabetes. Finally, Alstrom syndrome presents with infantile cardiomyopathy, retinal dystrophy and infancy onset obesity, then insulin resistant diabetes in their teens. Mutations have been described in the ALMS1 gene, encoding a protein that localises to the base of cilia. It is thought to be involved in intracellular trafficking and transport. Patients show severe insulin resistance and features of the metabolic syndrome out of proportion to the degree of obesity. Each of the above syndromes have different natural histories to type 1 diabetes; different complications, and different management requirements. Diabetes has become a diagnostic challenge as well as a management issue. Children presenting with extra-pancreatic features need to be extensively investigated to reach a definitive diagnosis. In particular, development of auditory, ophthalmic, or renal abnormalities, or developmental delay, should prompt consideration of other diabetes subtypes.

S4

What are the differences in physiology of exercise in type 1 diabetes? Implications for clinical management of diabetes and sport

I. Galle

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The timing of diagnosis of type 1 diabetes often coincides with the period in which people are most likely to become interested in sporting endeavours. For many, continued participation in sport is an essential part of life; for a talented few, sports may offer the pathway to success and fame. However, the marked variation in blood glucose during and following exercise, with seemingly inexplicable hypo or hyperglycaemia, combined with poorer physical performance may be discouraging. As the metabolic response to exercise in health and with diabetes is different, it helps to understand the physiology of exercise (1). Variations in diabetes, which impact on the mobilisation of fuels and the control of blood glucose during exercise, have the potential to reduce performance and stamina, and increase the risk of hypoglycaemia. The most significant factor-altering metabolism during exercise in diabetes is that insulin therapy is injected subcutaneously, and insulin lies in depots, which takes time for both its absorption and dissipation (2). The counter-regulatory hormone response to exercise, essential for gluconeogenesis and
lipolysis may be impaired (3,4) reducing hepatic glucose production (5) with potential mismatch between glucose utilisation and production (6–8). Blood glucose tends to fall during prolonged exercise, with the risk of hypoglycaemia during exercise, but may increase with any exercise that is short, but intense, or has elements of repeated short bursts of effort, between low levels of effort, particularly if it is predominantly upper limb exercise. Treatment of the insulin treated sports person requires careful integration of the training and event plans, food intake, basal and bolus insulin requirement. The experience of outstanding athletes with diabetes is instructive. Sir Steven Redgrave (rowing Olympic gold medallist), Gary Hall Jnr (swimming Olympic Gold Olympic-medallist) and Rod Kafer (Rugby World Cup) each used very different treatment regimes to optimise their performance, because of the different nature of each sport. People with uncomplicated type 1 who want to start, or continue in their chosen sport, can be encouraged to do so. Appropriate education of the person with diabetes and support by their healthcare professional is necessary, and careful consideration of the nature of the sport is required. Further research into the most appropriate strategies for insulin therapy and carbohydrate intake in the era of modern insulin, and on the role of different fuel metabolism in diabetes are required. The gain for people with diabetes is substantial, and the skills acquired by the healthcare professional are like to assist in the management of all people with diabetes.

References:

S5
Nutritional management of exercise, theory into practice.
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Nutritional management of exercise in children and young people with type 1 diabetes has developed from simple advice based on preventing exercise related hypoglycaemia. The development of our knowledge about the effects of carbohydrate foods through the glycaemic index, allows more appropriate advice about food choices to be given. Increased understanding of the physiology of exercise in the young person with diabetes, allows us to tailor our advice to the individual according to their sport and diabetes management. The registered dietician, with an understanding of exercise physiology, sports nutrition and diabetes management is in a unique position to provide advice which ensures the young person meets the needs of growth and development, achieves a carbohydrate intake which promotes both performance and repletion of glycogen stores post exercise, and helps to manage the glycaemic consequences of exercise. The aim of this session is to provide examples from clinical practice of the nutritional considerations for those involved in the management of a young person’s diabetes to ensure that glycaemic control & growth are not compromised, and sporting achievement is enhanced.

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S6
Preventing hypoglycaemia and maximising young peoples’ performance in sport
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The benefits gained from regular physical activity in children and adolescents with diabetes include improved cardiovascular fitness, increased lean mass, improved blood lipid profile, increased insulin sensitivity, decreased body adiposity and enhanced psychosocial well being (1). Unfortunately, improved blood glucose control does not always occur in youth with type 1 diabetes, despite improved insulin sensitivity and an increase in carbohydrate utilization with exercise, likely because they increase food intake to help offset the elevated risk for exercise-associated hypoglycaemia. Fuel metabolism during exercise differs markedly among healthy adolescents, children and adults. Compared with adults, children appear to have reduced utilization of carbohydrate stores and an enhanced ability to oxidize fat as fuel (2). Adolescents and children also tend to rely more on ingested carbohydrate than on carbohydrate stored within their bodies, which suggests that they have an immature glycolytic system (2). Children and adolescents with type 1 diabetes have similar fuel oxidation rates during exercise as non-diabetic children (3) but typically have large reductions in blood glucose levels during aerobic exercise, particularly if proper insulin and or carbohydrate intake strategies are not implemented (4,5). Increased carbohydrate intake just prior to and during exercise may be particularly useful in preventing hypoglycaemia in active children with type 1 diabetes since their activities may be unplanned and of an unpredictable intensity and duration (4). The amount of carbohydrate needed to limit the drop in blood glucose depends largely on the mass of the child and on the energy expenditure of the activity (1). Tables of
Invited Speakers

exercise exchanges are now available to aid diabetes health care workers and physicians on the carbohydrate requirements of youth (1). As an alternative to increased carbohydrate intake, a reduction in pre-exercise insulin dosage of 50-100% may be needed to help limit hypoglycemia during exercise in youth with diabetes. In children with type 1 diabetes on insulin pump therapy, stopping basal insulin delivery during exercise reduces significantly the risk of hypoglycemia (6). Unfortunately, nocturnal hypoglycemia is particularly common in active youth with diabetes (7), and the clinical management of this adverse effect of exercise is particularly challenging. As such, children and adolescents engaged in vigorous physical activity must be controlled vigilantly through individualized modifications in insulin therapy and nutritional intake so that the benefits of exercise out way the risks of hypo and hyperglycemia. This session will outline strategies for the prevention of hypoglycemia during and after exercise in active youth with type 1 diabetes using the exercise exchange concept. The presentation will also highlight the usefulness of continuous glucose monitoring systems for mapping glucose excursions caused by endurance exercise.

References:

S7
The EURODIAB network: Why and how?
G. Soltész

Department of Pediatrics, University of Pécs, Hungary on behalf of the EURODIAB Study Group

EURODIAB (EUROpe and DIABetes) was established (by Anders Green in 1988) to characterize the epidemiology and aetiopathogenesis of childhood Type 1 diabetes. A collaborative network of 44 centres using standardized procedures and protocols subsequently started the registration of newly diagnosed children with Type 1 diabetes covering about 30 million children and representing most European nations. Presently, the database contains the records of over 40,000 cases. The analysis of the EURODIAB data has revealed that the annual incidence in Europe varied more than tenfold between centres roughly following a North-South gradient. The analyses of the 5, 10 and 15 year periods clearly showed an increasing trend in the incidence rate, the overall annual increase being around 3%. Central Eastern Europe showed the highest rate of increase. There was no evidence of differences in trends by gender. In most centres the highest rate of increase was in the youngest age group (0–4 year). Apart from descriptive epidemiology, detailed modelling and a study of early mortality (vide infra), analytic (case-control) studies have identified or confirmed a number of susceptibility and protective environmental factors such as maternal age, birth weight and length, early nutrition and growth, vitamin D and atopic diseases. Earlier literature revealed that childhood Type 1 diabetes was a rare disease until the mid-century with upturn towards the final decades of the 20th century as documented by many studies including the EURODIAB network. With the present rate of increase, the incidence will double in 20–25 years mainly affecting younger and younger children, thus presenting an 'increasing' challenge for the community of paediatric diabetologists.

S8
Incidence rates of childhood diabetes in Europe: the importance of proper tabulation and analysis
J. Svensson, B. Carstensen, C. Patterson, G. Dahlquist, J. Rosenbauer & E. Gyllén on behalf of The EURODIAB Study Group

Introduction: The tradition in childhood diabetes epidemiology has been to describe incidence rates using 5-year age classes. The aim of this study was to tabulate data in one-year classes and use detailed modelling to analyse incidence rate and compare the results with the traditional modelling.

Materials and methods: Incidence data from 10 European centres participating in the EURODIAB collaborative group, covering new cases of type-1 diabetes age less than 15. Data were analysed using Poisson regression. We modelled the rates by a log-linear model with effects of age, period and cohort, using the mean of these three variables for each triangle in a Lexis diagram.

Results: The age-specific incidence curves were very similar between centres. The age-specific curve for girls was significantly different from boys in the detailed modelling, the traditional modelling in 5 year age classes, revealed no differences between gender. The increase over time was close to linear, only two centres showed a significant non-linear cohort or period effect.

Discussion: Since the increase over time was close to linear in all centres the detailed modelling was unable to describe the time changes significantly better than the traditional modelling. The age-specific changes in incidence rates, though, were well described by the detailed modelling since gender differences were revealed by this modelling. In studies covering longer time spans time changes in incidence would be suspected to be non-linear and therefore the detailed modelling would be superior to show exact timing of changes leading to better changes of detecting responsible risk factors.

S9
The age at diagnosis of type 1 diabetes continues to decrease in Belgian boys but not in girls: a 15-year survey

Introduction: Both in Sweden and in Belgium a decreasing average age at clinical onset of type 1 diabetes has been reported. Preliminary Belgian data suggested that this anticipation occurred preferentially in boys.
Aims: To verify whether this sex-specific anticipation persisted during a 15-year observation period in Antwerp (>90% case ascertainment) and in the whole of Belgium (>50% case ascertainment).

Methods: In Antwerp, we studied incidence trends between 1989 and 2003 in 746 type 1 diabetic patients under age 40. For 2928 antibody-positive patients diagnosed nationwide during the same period, age at diagnosis was analysed according to sex and calendar year.

Results: In Antwerp, the incidence of type 1 diabetes diagnosed before age 40 averaged 10.5 x (10^9) inhabitants^-1 x year^(-1) (95% CI: 9.8–11.3) and has not changed over this 15-year period. The incidence under age 15 increased significantly at the expense of the incidence in the age group 15–39 years (Poisson; p = 0.001). The increase under age 15 was almost exclusively restricted to boys under age 10 where the incidence more than doubled during the 15-year period (6.8 [4.1–10.7] in 1989-1993 vs. 17.2 [12.7–22.9] in 1999–2003; p < 0.001). Such an increase was not noted in girls under age 10 (p = 0.54). This selective trend toward younger age at diagnosis in boys was confirmed in the larger group of 2928 antibody-positive Belgian patients. The median age (interquartile range) at diagnosis decreased in boys – but not in girls – from 20 years (12–28) in 1989–1993 to 15 years (8–25) in 1999-2003 (p < 0.001). Multivariate analysis indicated that calendar year, indices of more severe and abrupt clinical presentation, insulin requirements, multiple antibody positivity and HLA-DQ2/DQ8 genotype were all independent predictors of early clinical onset.

Conclusions: Over a 15-year observation period a selective anticipation of clinical onset of type 1 diabetes was found in boys but not in girls. This earlier manifestation accompanied by a more severe metabolic dysregulation is likely to further increase the burden of diabetes.

S10 EUROCIB study of early mortality in type 1 diabetes diagnosed in childhood


Aims: To provide a contemporary picture of mortality in Europe in the years following type 1 diabetes diagnosed before the 15th birthday.

Materials and methods: Eleven population-based EURODIAB registers followed up 23 500 children diagnosed since 1989 either by record linkage to population registers or through contact with doctors providing patient care.

Results: There were 107 deaths during 167 265 person years follow up, approximately twice the 51.9 deaths expected from national mortality rates. The standardized mortality ratio (SMR), the ratio of observed to expected deaths, varied from under 1 to 4.7 between countries. There was little relationship between a country’s SMR and its incidence rate or Gross Domestic Product (GDP per capita). Over a third of deaths could be directly attributed to diabetes, while many others were due to accidents or violence. Small numbers of deaths without any cause determined at forensic autopsy (‘dead in bed’) were also reported.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Cases</th>
<th>Registrations</th>
<th>Person years</th>
<th>Observed deaths (O)</th>
<th>Expected deaths (E)</th>
<th>SMR = O/E (95% CI)</th>
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<tbody>
<tr>
<td>Lithuania</td>
<td>1006</td>
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<td>15</td>
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<tr>
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<td>443</td>
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<td>4069</td>
<td>10</td>
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<td>4.7 (2.3, 8.7)</td>
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<tr>
<td>Hungary (ex. Budapest)</td>
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<td>13 341</td>
<td>45</td>
<td>4.5</td>
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<td>1989-2002</td>
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<td>5027</td>
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Conclusion: Before the onset of late complications, significant excess mortality among type 1 diabetes mellitus cases diagnosed in childhood persists even in recent years. Variability in this excess mortality over different centres cannot be explained in any obvious way. Many of the deaths caused by diabetes in this age-group should have been avoidable.

S11 How to slow the accelerating incidence of type 1 diabetes with the least harm?

G. Dahlquist

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There is little support that the increasing incidence of childhood diabetes and the shift to younger age at onset is driven by environmental risk factors associated with the initiation of autoimmunity such as virus infections or early feeding patterns. The observations from epidemiological studies within the EURODIAB network rather suggest that risk factors which may accelerate already ongoing beta cell destruction and which show a steady increase in the population may cause this time trend. There is increasing experimental evidence that overload of the beta cell may be of importance also for Type1 diabetes since overload may sensitise the beta cell to immune damage and apoptosis. Overfeeding already during foetal life may prime the development of a beta cell phenotype more liable to apoptosis and necrosis and more sensitive to glucose stimulation. An increased body mass, over eating, sedentary life style, psychological stress, infection, inflammation and a high growth rate during puberty assert the same effect though overload but by different mechanisms. Trials trying to stop or arrest an already ongoing autoimmune process through immune modulation have so far not been successful. Such intervention also must be safe enough to be given to healthy children, which in fact may not be at risk. Interventions using metformin have been suggested but are potentially harmful. In the interim we may rather approach the overload factors in public health programs targeting the pregnant mother and the family with a newborn child. To change feeding patterns and sedentary life styles in this period of life would potentially be more successful than intervening later in life. Such intervention should be safe and would influence not only future risk of type 1 diabetes but also type 2 diabetes and other major threats to adult health. Such an approach according to the EURODIAB data would perhaps save
around 20% of cases of childhood type 1 diabetes and thus potentially stop part of the increase in trend.

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S12
Coeliac disease in diabetes mellitus type 1
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Coeliac disease (CD) is characterised by an immune mediated enteropathy of the small intestine. CD occurs in genetically predisposed individuals after ingestion of prolamins present in dietary grains. CD leads to a spectrum of mucosal changes ranging from IEL to villous atrophy and flattening of the mucosa. Treatment requires removal of gluten and related proteins from diet (GFD) and results in complete recovery of the small intestine damage. Clinical presentation of CD and age of onset of symptoms have changed during the last two decades and varies from severe malabsorption to atypical and silent forms with only subtle features as growth delay, abnormalities in bone mineralisation or infertility. The diagnosis of CD requires the detection of CD-associated autoimmunity with EMA or ATGA and a small intestinal biopsy showing the characteristic histopathological changes. Approximately 5–10% of patients with type 1 diabetes mellitus (T1DM) develop positive EMA or ATGA and about 2–5% have typical abnormalities on small bowel biopsy. Several patients present CD specific autoantibodies already at manifestation of T1DM, but a subset of patients become antibody positive later up to several years after diabetes onset. In most instances diabetic patients suffer from atypical or silent CD only detected by autoantibody screening. The co-occurrence of both diseases may be explained by a similar genetic background, and a certain degree of susceptibility to both diseases is associated with HLA-DQ2 and HLA-DQ8. Data on a possible influence of CD in DM are scarce and inconclusive. Several studies observed a negative impact on growth and weight gain. Controversy exists regarding the role of GFD on metabolic control in children with CD and T1DM. As GFD represents an additional burden on young patients with T1DM extended follow-up studies are needed to document the clinical benefit of CD screening and treatment in diabetic patients.

S13
Cystic fibrosis related diabetes
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Cystic fibrosis related diabetes (CFRD) is the most common comorbidity affecting the 22 000 CF patients entered in the Cystic Fibrosis Foundation Patient Registry. At the University of Minnesota, diabetes is seen in 9% of CF children, 26% of adolescents, 35% of adults age 20–29, and 43% of adults age 30 and older. Of those with diabetes, approximately one-third have fasting hyperglycemia and two-thirds have diabetes without fasting hyperglycemia. Fasting hyperglycemia may be chronic or may be intermittent with infection or glucocorticoid therapy. Aetiology: The primary cause aetiology is insulin deficiency due to loss of islets. Insulin resistance may also play a role in the development of CFRD, especially during acute infection. We envision a continuum of glucose tolerance in CF ranging from normal glucose tolerance, to increasingly severe glucose intolerance, to diabetes without fasting hyperglycemia, to diabetes with fasting hyperglycemia. At baseline, patients are insulin sensitive, and their place on this spectrum is determined by their insulin secretory capacity. During acute infection or glucocorticoid therapy, patients become more insulin resistant and move towards the right (diabetes) end of the spectrum; when the stress resolves, they move back to their baseline. Thus, the acute infectious status of the patient always needs to be considered when evaluating CFRD. Diagnosis: CFRD is often insidious in onset and may have been present for years before diagnosis. Potential symptoms of CFRD include polyuria and polydipsia, failure to gain or maintain weight despite aggressive nutritional intervention, poor growth velocity, unexplained decline in pulmonary function, and failure to progress normally through puberty. While none of these symptoms is specific for CFRD, diabetes needs to be considered in the evaluation of patients with these problems. The diagnosis of CFRD is made using the standard fasting or casual glucose or OGTT criteria for all forms of diabetes. Isolated impaired fasting glucose is extremely uncommon. Haemoglobin A1c is not an appropriate screening test for CFRD, since it is spuriously low in CF. Outpatient Management of CFRD with Fasting Hyperglycemia: CFRD patients are best treated in the diabetes team setting. The patient and his or her family are vital members of the treatment team. The goals of treatment are: Maintain optimal nutritional status, including normal growth and development in children and adolescents, and achievement/maintenance of normal weight in adults. Control hyperglycemia to reduce acute and chronic diabetes complications. Avoid severe hypoglycemia. Promote the optimal psychological, social, and emotional adaptation to living with diabetes. Be as flexible as possible within the framework of the patient’s lifestyle and CF. At present, insulin is the only medical therapy recommended for CFRD. Many different insulin regimens are possible, depending on the needs of the patient. Oral diabetes agents are not recommended in CFRD except in the context of research studies. Anecdotal clinical experience suggests that they are not helpful in the patient with fasting hyperglycemia. Their role in CF patients without fasting hyperglycemia is more controversial. Studies are underway to determine whether oral diabetes agents in these patients improve insulin secretion and nutritional status. The dietary management of CFRD is critical for the health and survival
of these patients. Underweight is associated with significant mortality, and thus it is never appropriate to reduce calories. CF patients have low cholesterol levels and do not appear to develop atherosclerotic cardiovascular disease, so fat restriction is not necessary. The method of carbohydrate counting (matching insulin dose to grams carbohydrate) allows the patient maximum flexibility to adjust their pre-meal insulin dose according to their appetite. Inpatient Management of CFRD with Fasting Hyperglycemia: During acute illness, CF patients are insulin resistant and are at high risk for development of hyperglycemia. Screening for diabetes is important at this time. Often, the insulin requirements are extremely large, and an aggressive regimen is needed to bring glucose levels under control. Prognosis: The additional diagnosis of diabetes is associated with significantly increased morbidity and mortality in CF, especially in women. Both the severity of glucose intolerance and the degree of insulin deficiency correlate with the rate of decline in pulmonary function. Insulin deficiency in CF may lead to abnormal protein catabolism, and thus negatively influence weight, pulmonary function, and ultimately, survival.

S14
Diabetic ketoacidosis related cerebral oedema
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Traditional acid-base analysis of plasma examines how PCO₂, bicarbonate concentration ([HCO₃⁻]), negative logarithm of the equilibrium constant (pKᵣ), and solubility of CO₂ (S₃C₀₂) interact to determine pH. In vitro, over the physiologic range, the log PCO₂ – pH equilibration curve for plasma is close to linear and this relationship can be expressed by the Henderson-Hasselbalch equation. An alternative acid-base assessment of plasma uses the relationship between PCO₂, net strong ion charge (equivalent to the strong ion difference, [SID⁺]), and the total plasma concentration of non-volatile weak acids ([A_total]) on pH (Stewart’s strong ion theory). In our reports (1,2) of hyperventilation, sodium is the major cation present in CSF. Its normal range is similar to that of plasma (133–145 mmol/l, mean 140 mmol/l), although the absolute concentration in CSF is slightly less when the difference in water content of the two fluids is taken into account. In DKA, at presentation, the ratio of [Na⁺]CSF to plasma [Na⁺] in one study of 10 patients was 1.13 ± 0.16 (mean ± SD). CSF Potassium: Compared with plasma, CSF has low K⁺ content that is little affected by changes in plasma level. In DKA, [K⁺]CSF was 3.2 ± 0.4 mmol/l over the plasma range 2.6–6.9 mmol/l. CSF Chloride: Chloride is the major anion of CSF and its concentration exceeds plasma level. Experimentally, in salt-depletion, CSF:plasma ratio of [Na⁺] remains within normal limits (1), while the corresponding ratio for [Cl⁻] increases from 1.2 (with a plasma [Cl⁻] of 112 mmol/l) to 1.7 (with a plasma [Cl⁻] of 53 mmol/l). Clinical implications: If we consider that DKA is associated with significant salt depletion and that choroid plexus biology and CSF electrolyte kinetics are primed to maintain normal CSF level of [Na⁺] – [Cl⁻], then fall in CSF-PCO₂ is a necessary adaptation because fall in [SID⁺]CSF is due primarily to rising [KA⁺]CSF. However, in this state, acute hyponatremia may, because of decreased [SID⁺]CSF, result in cerebral oedema if pHCSF (7.26–7.34) cannot be defended by lowering CSF-PCO₂. This risk would be in keeping with previous reports of brain herniation and relative hyponatremia, or excess free water, during treatment of DKA. Similarly, there is a theoretical risk of decreased [SID⁺]CSF in saline-induced acute hyperchloremia. This problem has not been reported as associated with cerebral oedema in DKA, but a recent population-based study of the incidence and risk factors for cerebral oedema in DKA contains an interesting observation. Univariate analysis revealed higher sodium infusion rates – and presumably CT – in cases compared with controls (1.41 ± 0.75 mmol/kg/h v 0.88 ± 0.60 mmol/kg/h, p = 0.012). The potential risk of cerebral oedema in both hypernatremia and hyperchloremia may explain why Mel and Werther (3) found no major change in the incidence of cerebral oedema despite significant change in policy on fluid and salt replacement therapy. We wonder whether a new strategy, applicable to both of these extremes, may be to limit CT entry into CSF, i.e., to counter the effect of ketoacid-stimulated Na⁺-K⁺-2Cl⁻ cotransporter activity. In this regard, it is noteworthy that Lam et al. (4) have recently reported a reduction in cerebral oedema formation in rats with DKA treated with saline and insulin after intravenous injection of the Na⁺-K⁺-2Cl⁻ cotransport inhibitor bumetanide.

S15
Incidence and impact of eating disorders in adolescents with type 1 diabetes
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The combination of type 1 diabetes and an eating disorder in an adolescent patient presents a considerable clinical challenge. It has been suggested that diabetes is itself a risk factor for the development of clinical eating disorders. This presentation reviews a series of studies carried out over 15 years investigating the prevalence and clinical course of eating disorders in adolescents and young adults with type 1 diabetes. Previous studies had suffering from several methodological problems: often highly selected patient samples were recruited; control groups were often absent; and the tools for assessing eating disorder features were compromised by the presence of diabetes. Most early studies were cross-sectional in design. More carefully conducted longitudinal studies have now shown that, whilst the overall prevalence of frank clinical eating disorders is probably not raised to any great extent at any given age, since the eating disorder features can fluctuate in severity over time, and even a brief period of disturbed eating habits and attitudes can lead to significant and lasting damage to physical health, the impact of such disorders is considerable. Attention now needs to be given to attempts to intervene to prevent the development of eating disorders in adolescents with type 1 diabetes, and to mitigate their consequences if they do develop.

S16
Natural history and family relationships of eating disorders in adolescents with type 1 diabetes
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We have conducted a program of research over the past two decades aimed at identifying the nature and specificity of the relationship and the medical and psychosocial factors associated with eating disorders (ED) in girls and young women with type 1 diabetes mellitus (DM). We have postulated that aspects of DM and its treatment interact with other factors to lower the threshold for expression of ED in this high-risk group. Research conducted by our group and others has allowed us to reach the
following evidence-based conclusions: (i) ED and their sub-threshold variants are more common in adolescent females with DM than in their non-diabetic peers. In a large, multisite case-controlled study of 356 adolescent girls and young women with DM and 1,098 matched controls, the prevalence of both full syndrome and subthreshold ED was twice as high in girls with DM compared to their non-diabetic peers (10% vs. 4%) (Jones et al., 2000). These ED fall largely into the categories of bulimia nervosa and its sub-threshold variants, and eating disorders not otherwise specified. Further, in a case-controlled study of 101 preteen and young teenage girls with DM, and 303 age-matched controls, eating disturbances, though mostly mild, were identified in 8% of the DM sample compared to only 1% of their non-diabetic peers (Colton et al., 2004). (ii) ED are associated with higher HBA1c levels, and an earlier than expected onset of DM-related medical complications, particularly retinopathy. In a 4-year follow-up of 91 adolescent girls and young women with DM, ED were common, persistent and associated with poor metabolic control and a 3-fold increase in the risk of retinopathy 4 years later (Rydall et al., 1997). HBA1c levels were significantly higher among those girls classified with highly disordered eating at baseline (11.1%) and follow-up (9.7%) compared to those with non-disordered behaviour at baseline (8.6%) and follow-up (8.2%). Some degree of retinopathy (mild background retinopathy or worse) was present at follow-up in 86% of young women with highly disordered eating at baseline, compared to 43% with moderately disordered eating and 24% with non-disordered eating. (iii) Adolescent girls and young women with DM frequently use deliberate insulin omission or dosage manipulation for weight control or weight loss through induced hyperglycemia and glycosuria. Two percent of preteen and young teenage girls (age 9–13) (Colton et al., 2004), 11–14% of adolescent girls (age 12–19) (Rodin et al., 1991; Jones et al., 2000) and 34% of older adolescents and young women (age 16–22) (Rydall et al., 1997) reported this dangerous weight control behaviour. Apart from dieting, deliberate insulin omission is the most commonly employed weight control strategy among adolescent girls and young women with DM. (iv) The quality of the family environment, maternal weight and shape concerns, and eating disturbances in adolescent girls and young women with DM are closely interrelated. In a series of observational studies (Maharaj et al., 1998, 2001, 2003, 2004), disturbances in mother-daughter interactions, and maternal weight and shape concerns, were linked to eating disturbances and impaired metabolic control in teenage girls with DM. Further, in our longitudinal study of preteen and early teenage girls (Colton et al., submitted), specific family factors (more problematic relationship with parents and more disturbed maternal eating attitudes) and individual factors (higher BMI, lower self-esteem and more depressive symptoms), were identified as predictors of eating disturbances in this high-risk group. (v) The value of interventions to treat or prevent ED in girls and young women with DM is largely unknown. Our group conducted a randomized, controlled psychoeducational (PE) intervention targeting eating disturbances in adolescent girls with DM (Olmsdell et al., 2002). PE was associated with reductions in dieting, body dissatisfaction and preoccupation with thinness and eating, which were maintained at 6 and 12 months. However, this brief intervention did not result in significant improvements in metabolic control or insulin omission for weight control. In conclusion, ED is common and persistent in girls and young women with DM, and are associated with impaired metabolic control and serious DM-related complications. Health professionals involved in the care of girls and young women with DM should maintain an index of suspicion for the presence of an eating disturbance, particularly among those with persistently poor metabolic control and/or weight and shape concerns.

**Invited Speakers**

The Hvidøre study group on childhood diabetes and the remission phase study

H. B. Mortensen, Chairman Hvidøre Study Group 1994–2005 on behalf of Hvidøre Study Group on Childhood Diabetes

The Hvidøre Study Group on Childhood Diabetes evolved in 1994 during a workshop to discuss strategies that might be important in improving the quality of paediatric diabetes care. The name is taken from the house where the annual meetings are held. Hvidøre is a stately country mansion, which for 50 years was used as the Novo diabetes hospital. It is now a training and conference centre owned by Novo Nordisk A/S working in partnership with the Study Group. It is an international study group covering 22 paediatric centres from 18 countries across Europe, Japan and North America. The mission of the Hvidøre Study Group: An international study group committed to multi-centre collaborative research to improve diabetes care for children and adolescents. The aim of the Hvidøre Study Group is to i) Stimulate research ii) Improve the quality of care iii) Disseminate knowledge of childhood diabetes. The Hvidøre Remission Phase Study is a prospective, long-term observational study conducted in 18 centers representing 15 countries in Europe and Japan. All children aged less than 16 years with newly diagnosed diabetes presenting to the paediatric departments of the participating centres between August 1999 and December 2000 were eligible for the study. Clinical information and blood samples were collected from 275 children and adolescents age < 16 years with newly diagnosed type 1 diabetes. Year of birth, sex, and insulin dose were recorded. Hba1c and C-peptide were analysed centrally. A stimulated C-peptide test was carried out in each subject at 1, 6 and 12 months after diagnosis and serum for immunology and HLA typing was collected. The major clinical end points of this study are reported here. The residual C-peptide level was significantly related to the age at onset of the patient. C-peptide secretion at each time point of follow-up was lowest for patients in the youngest age group and highest in the pubertal children (10–15 years). The levels reduced similarly in all patients regardless of age during the first year after diabetes onset. The unadjusted Hba1c level was markedly elevated at the time of diagnosis in all age groups (0–4.9 years: 10.3%, 5–9.9 years: 11.0%, 10–14.9 years: 11.7%, p = 0.0005). These levels declined and reached a minimum within three months in all subjects (0–4.9 years: 7.4%, 5–9.9 years: 6.8%, 10–14.9 years: 6.9% , p = 0.0092). Subsequently the Hba1c levels gradually began to rise in all age groups over the next 3–12 months. The mean insulin dose decreased in the children above 5 years of age during the first 3 months and subsequently increased gradually while children below 5 years of age showed a continuing increase throughout the 12 months period. The mean insulin requirement was significant lower (p = 0.0197) at 6 months in the 5–10 years compared to the two other age groups. Definition of partial remission: Traditional definitions of the remission phase include mostly the insulin dose alone or the dose in combination with Hba1c. Since Hba1c is influenced by the insulin dose and these two parameters cannot be regarded separately, we used a joint expression, which includes both parameters:

Insulin dose-adjusted Hba1c = Hba1c + 4x insulin dose in units/kg/24 hours < 9%.

According to the insulin dose-adjusted Hba1c definition the prevalence of partial remission was significantly higher after 3 months (p = 0.0258), 9 months (p = 0.0054) and 12 months (p = 0.0475) in school age children (5–10 years) and pubertal patients (10–15 years) compared to the very young children.
(0–5 years). **Definition of diabetic ketoacidosis (DKA) at onset.** Mild ketoacidosis (HCO₃⁻ 10 – ≤15 mmol/l or pH 7.2 – 7.3) was recorded in 6.9%, moderate ketoacidosis (HCO₃⁻ 5 - ≤10 mmol/l or pH 7.1 – 7.2) in 7.6% and severe ketoacidosis (HCO₃⁻ ≤5 mmol/l or pH ≤7.1) in 6.2% of patients. While any degree of ketoacidosis was present in 20.7% of patients, 73.8% displayed a normal acid-base status at onset (no information available in 5.5% of patients). DKA at onset was associated with a reduced stimulated C-peptide level 1, 6 and 12 months after diagnosis and children without ketoacidosis at diagnosis (standard bicarbonate above 15 mmol/l) had on average a higher rate of remission than those with DKA. **HbA1c at onset – its effect on later control.** By stepwise multiple regression analysis HbA1c% at onset was found to be the only significant predictor of HbA1c one, two, and four years after diagnosis when sex, age, standard bicarbonate, initial blood glucose, number of injections and insulin dose were included as co-variates in the statistical analyses.

**Conclusion:** The new definition of remission is convenient and easy to use. Partial spontaneous remission is less frequent in very young (0–5 years) and pubertal patients (10–15 years) compared to school children aged 5–10 years. The low residual beta cell capacity as assessed by stimulated C-peptide that characterizes the diabetes of the very young patients may be responsible for reduced remission in this group, while the low insulin sensitivity that characterizes the pubertal state explains the lower rate of remission in the pubertal patients despite a consistent residual insulin secretion. Since clinical remission reflects preserved beta cell mass which protects the patient from developing DKA, children with DKA would expect to have a lower percentage of viable beta cells at the time of diagnosis. This is in agreement with a significant proportion of the children without ketoacidosis entering remission in the early phase of the disease. Rather surprisingly, we have also found that the HbA1c at the time of diagnosis appears to affect later metabolic outcome.

**Key references:**

**S18 Exploring and explaining center differences?**
C. de Beaufort, Luxembourg on behalf of the Hvidøre Study Group on Childhood Diabetes

**Introduction:** Two previous international cross-sectional studies from the Hvidøre Study Group showed persistent center differences in glycemic control. Although a significant difference in quality of life was observed in those adolescents with the better metabolic control, the lack of an explanation for the centre differences necessitated a third study, to explore again factors contributing to the metabolic outcome. Clinical data, questionnaires as well as a centralised HbA1c were collected. In the questionnaires, four major topics were included: lifestyle and well being, family structure and communication, team and services offered, as well as insulin management. Lifestyle items were taken from the mandatory questions in the WHO HBSC questionnaire, thus allowing comparison with the healthy background population (www.hbsc.org). Family functioning has been shown to play a major role in therapy adherence and metabolic outcome (1). The influence of the team and its services may play a crucial role and needed to be evaluated carefully. Finally, the real implementation of the complex insulin management required further investigation to develop, if necessary, modified education strategies.

**Results:** Questionnaires from 2062 adolescents (age: 14.4 ± 2.3 years; 49.4% female; diabetes duration 6.1 ± 3.5 years) from 21 centres in 17 countries were completed. Mean HbA1c was 8.2 ± 1.4% with the persisting significant difference between centres ranging from 7.4 to 9.3%. Ranking of those centres, which have participated, previously (n = 14) remains the same. Although metabolic control in individuals was influenced by lifestyle effects, only a marginal impact on the centre differences was observed. Parental status, as well as disagreement between adolescent and parent on blood glucose monitoring had a significant influence on HbA1c. These effects do not reduce the impact of the centre per se. Presence of a 24h hotline may improve outcome slightly, but target setting plays a more important role in explaining centre differences. Insulin regimens varied considerably and had some impact on HbA1c (eg twice daily free mixing but only in 7% of the children). Of more importance are the adjustment strategies (insulin, food and blood glucose measurements), which have a major impact on outcomes.

**Conclusion:** Centre differences persist. Initial evaluation of the data indicates the effects of lifestyle, family structure, team services and diabetes management including target setting and dose adjustment. Further analysis is necessary to investigate the role of education strategies in optimising diabetes outcomes.

**References:**
S19
Exploring the impact of diabetes susceptibility genes on disease progression and glycaemic control in a cohort of children and adolescents with newly diagnosed type 1 diabetes
L. Hansen, S. Poerksen, P. Hougaard, R. W. Holl, P. G. F. Swift & H. B. Mortensen on behalf of Hvidøre Study Group on Childhood Diabetes

Type 1 diabetes is an autoimmune disease with selective loss of pancreatic beta-cells. Type 1 diabetes is also a multifactorial disease caused by both environmental and genetic factors and four genes: HLA-Class II (IDDM1), insulin (IDDM2), CTLA4 (IDDM12), and the lymphoid-protein tyrosine phosphatase (LYP/PTPN22) have consistently been associated with increased risk of developing type 1 diabetes. The role of these susceptibility genes in disease pathogenesis and progression are, however, not well investigated from a clinical perspective, and recently, other non-immune genes that are classical drug targets for type 2 diabetes: peroxisome proliferator-activated receptor-g and ATP-sensitive K^-channel Kir6.2 have also been associated with type 1 diabetes and neonatal diabetes. The aim of our study was to investigate in a prospective setting the impact of these genes on disease progression (residual beta-cell function, autoantibody presentation, cytokine activities) and glycaemic control in children and adolescents with newly diagnosed type 1 diabetes. The Hvidøre remission phase study. A multi-centre longitudinal investigation with 18 participating paediatric centres from 15 countries. 275 children and adolescents <16 years with newly diagnosed type 1 diabetes were followed for 12 months after diagnosis. A stimulated C-peptide test was carried out in each subject at 1, 6 and 12 months after diagnosis and serum for immunology and genetic analyses was collected. HbA1c, analysed centrally, was determined at 0, 1, 3, 6, 9, and 12 months after diagnosis. Diabetes genes and disease progression. We investigated the autoimmune activity (ICAs, GADAs, and IA-2As) in addition to insulin antibodies and HLA haplotypes as predictors of residual beta cell function during 12 months in children and adolescents. ICA, GAD and IA2 mostly decreased over the 12-month period. Insulin antibody positivity increased from 1 to 6 months. We found that positivity for three pancreatic islet cell autoantibodies at 12 months was associated with poor beta-cell function and high levels of insulin antibodies were associated with increased daily insulin requirement. However, we found no association between HLA-risk haplotypes and residual beta-cell function at any time. Susceptibility to type 1 diabetes in the insulin gene is contributed by the variable number of tandem repeats (INS VNTR) upstream of the gene. High numbers of repeats (class III alleles) associate with protection and low numbers (class I alleles) with susceptibility. Reduced autoimmune reactivity towards insulin, secondary to increased expression of insulin in the foetal thymus, has been suggested as the protective mechanism conferred by the class III alleles. We investigated the association of the INS VNTR class III allele (23Hphl) with insulin antibody presentation and residual beta-cell function during the first 12 months after diagnosis. The insulin antibody titres at 1 and 6 months were significantly lower in the class III/III and class I/III genotype groups compared with the class I/1 genotype group. Residual beta-cell function 12 months after diagnosis was twice as high among class III/III genotypes compared with class I/1 and class I/III genotypes. Furthermore the class III/III genotype had a 1.1% reduction in HbA1c after adjustment for insulin dose. These findings indicate a direct connection in vivo between the INS VNTR class III alleles, a decreased humoral immune response to insulin, and preservation of beta cell function in recent-onset type 1 diabetes. We investigated the CTLA4 (+49GA/Thr17A1a) and found that the homozygous Ala/Ala carriers had significantly higher rate of ketoacidosis and presented higher number of GAD antibodies after 12 months disease, but we found no impact of the LYP/PTPN22 on disease presentation or progression. Does the entero-enteric axis also play a role in disease pathogenesis? The Kir6.2 is expressed in the pancreatic beta-, alpha and delta-cells, the entero-enteric L cell in the distal gut and in the appetite-regulating center of the brain. We investigated whether the Glu23Lys variant in the Kir6.2 has influence on residual beta-cell function, glucagon secretion, GLP-1 release and the overall metabolic regulation. Carriers of the variant had a tendency towards a reduced stimulated serum GLP-1 level and higher meal stimulated glucagon release. The residual beta-cell function, however, was probably too small to see a difference in stimulated serum C-peptide level. Interestingly, HbA1c (adjusted for insulin dosage) was significantly increased for those carrying the variant. The study indicates that the Kir6.2 variant might play a central role for blood glucose regulation in the remission phase probably by altered GLP-1 activity on the gut with faster absorption of nutrients and an increased postprandial glucagon level.

Conclusion: The study shows that genetic sciences successfully can be integrated into clinical studies and provide new knowledge of the progression and treatment of children and adolescents with new onset diabetes.
GLP-1-Based antidiabetic therapy
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Oral glucose ingestion leads to higher insulin secretory responses than does an intravenous glucose infusion, even with a similar glycaemic profile, in healthy subjects. This ‘incretin effect’ is responsible for 20–60% of insulin secretory responses after oral glucose, and probably also after mixed meals. Mediators of the incretin effect are intestinal hormones like glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide; GIP) from the upper gut, and glucagon-like peptide 1 (GLP-1), mainly produced in the lower small intestine. These incretin hormones are secreted in response to nutrient (glucose, triglycerides) ingestion and augment glucose-induced insulin secretion through receptors on pancreatic endocrine B cells. In patients with type 2 diabetes, this incretin effect is reduced or absent. The reason is a somewhat reduced meal-related GLP-1 secretion and an impaired insulinotropic action of incretin hormones, especially of GIP, which has lost most of its activity in type 2-diabetic patients. The insulinotropic action of GLP-1 is much better preserved in patients with type 2-diabetes. GLP-1 (a) stimulates insulin secretion in a glucose-dependent manner, (b) suppresses glucagon, (c) reduces appetite and food intake, (d) decelerates of gastric emptying, and (e) stimulates pancreatic B-cell neogenesis, growth and differentiation in animal and tissue culture experiments, and (f) inhibits B-cell apoptosis in vitro. Intravenous GLP-1 normalizes and subcutaneous GLP-1 significantly lowers plasma glucose in the majority of patients with type 2-diabetes. GLP-1 itself, however, is not useful for chronic antidiabetic treatment, because it is too rapidly inactivated by proteolysis (dipeptidyl peptidase-4; DPP-4) and eliminated (via the kidneys) from the circulation. Agents interacting with GLP-1 receptors in pancreatic islets or the (central) nervous system have been found in nature (like exendin-4, from the saliva of the Gila lizard, Heloderma suspectum) or developed as ‘incretin mimetics’ (like liraglutide, slightly modified GLP-1 with a free fatty acid attached to promote binding to albumin and prolonging the pharmacokinetic half-life). Clinical trials with exenatide (two injections per day) and liraglutide (one injection per day) have shown reductions in glucose concentrations and HbA1c by up to 2%, associated with moderate weight loss, but also transient episodes of nausea. An alternative therapeutic approach is the inhibition of DPP-4 by small molecules like vildagliptin or sitagliptin, which leads to higher increments in intact, biologically active GLP-1 after meals. The long-term administration of DPP-4 inhibitors as tablets has also been shown to reduce fasting and postprandial glucose concentrations as well as HbA1c values. Thus, correcting the characteristic defects in the entero-insular axis is a promising novel therapeutic approach to treat patients with type 2-diabetes. Whether these novel antidiabetic medications might also be used as an adjunct to insulin therapy in type 1-diabetic patients, is an open question. It is tempting to use GLP-1 receptor agonists to interfere with immune damage and resulting β-cell apoptosis, but - on the other hand - the stimulation of insulin secretion through GLP-1 receptors might make β-cells more vulnerable to immune attack. The balance of these two opposing influences is not known. Therefore, results from studies in type 1 diabetes early after diagnosis (i.e., with some preserved β-cell mass and function) and after islet transplantation need to be awaited, before recommendation can be made. In Europe, a first incretin mimetic (exenatide) and DPP-4 inhibitors (sitagliptin, vildagliptin) will probably become available in 2007.
modified for delivery in an individual and family therapy format. It has recently been adapted for delivery in the community as part of a randomised controlled trial (Rudolf et al – in press).

References
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W2
Energy balance and lifestyle interventions – innovative approaches
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Obesity among youth is a serious problem, leading to increased risk for chronic diseases like Type 2 diabetes. This presentation will review the influences on energy balance that will need to be addressed in intervention work, and identify innovative intervention channels. High-energy dense diets are usually high in fat. High intakes of dietary fat are positively associated with adiposity and weight gain among children (Robertson et al., 1999). Soft drink consumption is high among youth. In a longitudinal study, increasing soda consumption predicted the greatest increase of body mass index (BMI) among girls from 9 to 19 years of age (Striegel-Moore et al., 2006). Diets high in fruit and vegetables (FV) and complex carbohydrate foods tend to be low in fat. Inverse relationships between FV consumption and dietary fat intake, fruit consumption and percent of body fat, and vegetable consumption and lower BMI have been documented (Rolls et al., 2004). Family dietary counselling to increase FV consumption was more successful compared with families who were only encouraged to reduce high fat and sugar food consumption (Epstein et al., 2001). Snacking frequency is related to higher energy intakes. Fast food/restaurant meals have been positively associated with fat and energy intake among youth and adults. Large portion sizes are a problem with many foods obtained away from home, and are related to increased energy intake (Rolls, 2003). Physical activity (PA) is associated with decreased adiposity among youth, whereas sedentary behaviour is associated with increased adiposity among youth (Salby et al., 2004). Therefore, prevention/treatment strategies to improve energy balance should target increasing FV consumption, substituting water for sweetened beverages, encouraging healthy snacking behaviours, controlling portion sizes and making more healthful food choices away from home, and increasing PA and decreasing sedentary behaviour. Families are a critical target for interventions because the home environment is where children learn and practice dietary and physical activity behaviours (Birch and Fisher, 1998). Observation of parental food selection and eating behaviours shapes child dietary behaviours (modelling) (Birch and Fisher, 1998). Parents also make foods available in both the home and outside-the-home environments, and are mainly responsible for home food preparation practices. Parental self-efficacy is needed so that parents are able to promote healthy home food environments. Parent feeding style may contribute to the development of obesity, if eating becomes a response to external cues of some sort like strict parental regulation (Cullen et al., 2000). Family-based weight management approaches that target parents and emphasize a healthy lifestyle and not weight reduction have been successful. Parents provide the healthy foods in the home and are a role model, providing a family environment that fosters healthy practices related to energy balance. Obesity prevention and treatment programs should use the most effective behavioural strategies to promote behaviour change, and be available and accessible to a wide population. The Internet is one channel that provides an interactive aspect to care, in a format widely used by both youth and adults. Significant increases were observed in FV consumption, physical activity, and FV self efficacy between baseline and post assessment for a group of 8–10 year old African-American girls who participated in an 8-session internet program promoting healthy eating and physical activity (Baranowski et al., 2004). The Family Eats web-based program, designed for African-American families to promote FV and lower fat food consumption, was successful at increasing parent-reported self-efficacy for menu planning and FV availability, modification of meat-fat practices, substitution-fat practices, and healthy restaurant selections. Daughters reported increased parent modelling of eating FV. Each of the 8 sessions includes a short photo-novella depicting a family food issue, a weekly activity/goal, an Opinion Poll requesting problem solving tips, and previous Opinion Poll results and tips. These results document the ability of web-based programs to influence mediators of dietary behavior change. Innovative yet comprehensive interventions enabling families to create healthy home environments will be critical to reversing the obesity problem. These programs need to be widely available and convenient to all, including those families most at risk.

References

W3
Diabetes in school ‘What care should we expect?’
M. Hallman
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The National Swedish Guidelines for treatment of diabetes in children and adolescents emphasize the necessity of education for teachers and ancillary staff in diabetes care. Every child and adolescent has the right to achieve a good metabolic control in order to prohibit acute and long-term complications and provide the utmost quality of life. The National Swedish Board of Health
and Welfare are responsible for hospital administration and check the quality of medical care given. They have given some advice ‘SOFS 1996:9 (S). Self-care in school’. This document says that self-care is not health care performed by health care professionals, but the task which responsible physicians normally give to a patient or his/her parents to perform. This means that parents can ask teachers and others in school to perform diabetes self-care. The teachers association in Sweden allows them to give injections and perform plasma glucose tests in school depending on their own free will. Twenty-five years ago in Sweden, diabetes self-care did hardly at all take place in the school setting. Injections twice or three times a day was regular treatment in T1DM. It was difficult for the parents and the child/adolescent to make school personnel understand the special needs for a child/adolescent with T1DM, especially how to handle hypoglycaemia. We started, year 1984, to invite school personnel to the hospital for diabetes information in order to promote the understanding of the essence of the disease and explain why it was important to take notice of and treat hypoglycaemia at once. Teachers often showed an explicit fear of severe hypoglycaemia with unconsciousness and sometimes they didn’t know how to handle the situation if it occurred. The problem for younger children who couldn’t perform injections and/or blood tests was focused. Multiple injections where introduced and valued as a much better way of treating diabetes. Frequent plasma glucose monitoring was eligible and metabolic control was expected to be increased, but who should be responsible for injections during daytime when the parents are not available? In the year 1988 we visited every school and preschool with a diabetes education program and now also put the question to the school personnel if they did feel secure to learn how to perform injections and testing plasma glucose. Many of them were positive when they understood the advantages for the child. We also pointed out the importance of sharing diabetes care with at least one other person close to the child, so the care didn’t depend on one person. Today we educate by visiting preschool for children ≤ 6 years of age and for all children and adolescents when needed. Once a year we also invite school personnel to attend, for half a day, a diabetes education program, performed by a physician, paediatric diabetes nurse and a dietician. When a child is diagnosed with T1DM we ask the parents to contact the school nurse because she/he has an important role in diabetes education in the school setting, not to forget the food service personnel. Most parents ask the diabetes nurse to contact the school nurse as well because they need support from the diabetes team. There is not much research done to evaluate the effectiveness of diabetes education for school personnel. The outcome of recent studies assessed school personnel’s limited knowledge of diabetes and found that school rules impeded self-care of diabetes. Children with diabetes felt supported in school but improvement in flexibility and individualisation of the self-care must be done. Parental anxiety to what extent and how self-care is provided is also reported. From the teachers point of view in a study for children with chronic health conditions including diabetes, two issues had the highest impact on teachers willingness to support diabetes self-care i.e. time to pay extra attention to the child and personal risk or liability. They were also afraid of classroom emergencies or death. If information is provided only by the parents there could be a hindrance for their concerns to be voiced and answered. Our experience is comparable to these findings but the major barrier is probably the fear of giving anybody an injection and/or perform plasma glucose test, because they are not trained to do this and consider it’s not their duty. The charge and the challenge for the diabetes team are to support both children/adolescents, parents and school personnel to facilitate appropriate diabetes care, even in the school setting. In The Convention on the Rights of the Child, article 24, it says ‘1. … the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health...and article 28 says ‘1. …the right of the child to education’, emphasize that.

W4
Lessons from the classroom: comprehensively addressing the needs of school children with diabetes by addressing school staff, parent and child management issues and emotional concerns
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Managing diabetes in children is a full-time job; it doesn’t stop when the child leaves the house. As a matter of fact, that’s really where the toughest part of the job begins—for both the children and their parents. The purpose of educating parents and children in the effective self-management of diabetes is multi-faceted; focusing on promoting optimal metabolic control as well as effective emotional and logistical coping with the daily challenges of integrating diabetes care into daily life. In children, who spend most of their waking hours in the school setting, it is imperative that the focus of effective overall management be extended to the school setting as well. Parents will have a difficult time ‘letting go’ and trusting their children to leave the home environment if teachers and school staff are not adequately trained and provided with the necessary resources to ensure optimal, seamless care while their children are in school. If school personnel aren’t educated and adequately trained, parents will feel apprehensive about their child being away at school during the day. This ‘anxiety’ has the capacity to affect the child’s school performance and socialization process if undue, additional tension characterizes the learning and school experience. Teachers and staff who are unfamiliar with and nervous about diabetes and its management in children need to be reassured with adequate training and support that these children and their medical concerns and general classroom learning goals are entirely reconcilable within the school setting. The Diabetes Program developed for the Oakland Unified School District, to address the needs of both type 1 and 2 diabetes in the school setting, was unique in being the first program of its kind in the United States to comprehensively assess and address the medical management and emotional concerns of all parties involved—children, parents, teachers, school administrators and community organizations. Its success was largely due to its broad view of those involved in the process, their specific needs and overall school system/educational goals of all involved. Its focus was on creating an atmosphere of understanding and support for children, their families and school personnel. It included counseling and education for families, teachers with a strong community-outreach educational component. Development of general guidelines and policies that adequately and sensitively addressed each segments’ needs and concerns was the primary focus, with the overall goal of providing a safe and ‘seamless’ educational atmosphere and experience. This program was developed prior to the development of the American Diabetes Association’s ‘Safe At School’ Program, served as an impetus to its development and included many of its components. Training sessions, for teachers and administrators, individual school health plans for children with type 1 and 2 diabetes, effective use of 504 Plans, Parent/Teacher Organization educational seminars, collaborating with community agencies and development of special programs within the school district were all a part of this multi-faceted approach. The program was so successful that it attracted the attention of local and national news media as well as the attention of the pharmaceutical industry which had the program continued would have resulted in large-scale program sponsorship. The program was extremely successful, based on clinical outcomes and feedbacks from
W5
Transition to adult care: ‘and now for something completely different’
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Diagnosis of type 1 diabetes is usually followed by years of intensive treatment with a paediatric health care team that can include a paediatric endocrinologist, a diabetes educator, a dietician/nutritionist, and a social worker. Paediatric care is usually intensive and comprehensive and tends to be parent-oriented, as parents usually have primary responsibility for management of paediatric chronic illness. When patients are asked to leave the paediatric clinic (frequently around age 18) they are transferred to an adult care physician, which can be a very different experience for both patient and parent. The transition to adult care is frequently accompanied by a failure to schedule or attend regular clinic appointments. This can be problematic; HbA1c values appear to peak in 18–19 year olds and irregular clinic visits have been associated with poor glycaemic control and a higher risk of ketoacidosis and retinopathy. Yet most paediatric diabetes clinics lack a good system for guiding this transition in responsibility. They may lack a method for identifying when youth are ready for additional responsibilities and when parents need to maintain or increase their participation. Limited research in this area suggests that there are individual and family characteristics that could predict problems with the transition (Ingersoll et al., 1986; Wysocki et al., 1992). There have been few studies identifying the best clinic model for the transition to adult care. Both parents and adolescents feel unprepared for and anxious about the transition. McGill (2002) suggests that preparation for the transition should begin in early adolescence and include: ‘self-advocacy, independent health care behaviours, sexual health, psychosocial support, education and vocational planning, and health and lifestyle (drug, alcohol, etc.)’ [P.66]. Kamboj (2005) suggests the importance of the paediatric diabetes care team preparing the adolescent for the transition by providing opportunities for the adolescent to practice problem-solving or troubleshooting major and minor problems in daily diabetes self management in order to enable the adolescent to build a sense of self-efficacy. There is some evidence that preparing the adolescent by introducing the patient to an adult diabetes care team prior to the transition improves the transition experience (Vanelli et al., 2004). One suggestion is a gradual transition in which both paediatric health care specialists and patients have confidence in the adult care physician. Solutions include transition clinics with paediatric and adult diabetes care teams and a transition coordinator. Viner (1999) suggests that the problem with the transition is that paediatric clinics tend to ignore the adolescents’ independence, reproductive and employment (adult) behaviour, while the adult clinic neglects developmental and family issues. Other issues include: timing of the transfer based on developmental readiness and health status; a preparation period (early adolescence) for establishing the necessary skills and education for independent self-management (education should provide an understanding of the disease, source of symptoms, treatment rationale, problem solving/management, and help-seeking/requests from health care professionals); and coordination between paediatric and adult care givers during the transition, possibly with joint staffing during the transition. Viner recommends a shift in responsibility to self-care as soon as the adolescent is ready with parents not required at the beginning of the clinic visit (but invited to join the session later) starting at age 13. Although Cameron (2001) focuses on children with renal disease, he provides recommendations for facilitating the transition that could easily apply to diabetes care (proactive discussion of the transition; spending time in adult unit; structuring adult care to spend more time with young patients; having physicians spend time in the alternative (adult/adult) unit; and tailoring the transition to the ‘psychosocial functioning, independence, and general maturity’ of the individual patient). Cameron concludes that the transition needs to be age-appropriate. Watson (2005), discussing how to facilitate the transition for patients that require renal care, emphasized: addressing psychological and social problems; readiness of youth (self-management); plan for future social support; implications for future education, employment, social and psychological development; and a developmentally-appropriate shift from compliance to adherence to concordance (shared agreement about treatment). While these studies provide a framework for examining the transition to adult care, issues that need to be addressed include: i) How can we determine when youth are ready for the transition to adult care? What are the essential characteristics of this readiness for adult care? Should the transition be age dependent or based on an evaluation of the youth and his/her family? ii) How can we prepare patients and parents for this transition? iii) What can the paediatric clinic do to facilitate this transition? iv) What can adult physicians do to facilitate the transition?

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W6
The diabetes centre—a potential advancement in transitional care
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Children with diabetes are traditionally cared for by the paediatric team up to the age of 16–18, but even this varies with some paediatric services continuing care beyond the teenage years. In many structures, diabetes care is then 'suddenly' the responsibility of the adult diabetes services. For the paediatric team who have invested considerable time and effort in supporting the family and know them well, transferring care to another team, often perceived as having a different philosophy of care, is not easy. Equally for the 'adult' diabetes team there is the challenge of receiving a reluctant young person often unprepared for self-management, the majority of the responsibility for diabetes care having previously been given to the parents. Often in the traditional model parental support is also suddenly undermined which may have deleterious effects. For the young person with diabetes, and to many parents, leaving the familiarity of the paediatric team to a clinic in a new location with new personnel is a daunting prospect. Furthermore, this occurs when other more important changes are occurring in the adolescent’s life. This is a time when they are striving to develop their own identity and independence and are having to cope with changes in psychological, social and sexual environments. For the parent this heralds a loss of responsibility for diabetes care and concerns that the young person will be ill prepared and not yet mature enough to take on self-management. Not surprisingly, this can be a time fraught with problems. Failure to attend clinics, deterioration in glycemic control, increased rates of ketoacidosis or even mortality often typifies the outcome of young people transferred to adult clinics. To solve some of the problems associated with transfer of care many services have established transition clinics where members of both paediatric and adult teams work together to facilitate a smoother hand over. This allows time for the young person and their parents to become familiar with the adult team. Although a step in the right direction, simply running a combined clinic, the only perceived change is a different appointment time (afternoon/evening rather than morning) to a clinic with their peer group and other young adults (16–25’s). Within this structure of care, transfer to the adolescent clinic can be based on a joint assessment of the youth’s developmental readiness independent of age. Our experience suggests that the Diabetes Centre is an ideal location for paediatric and adolescent clinics; it addresses many of the logistic problems associated with transfer of care, enhances team-working and supports the development of common philosophy of care.

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W7
Teachable moments: innovative education and support in pediatric diabetes care
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Glycemic control is a well-established predictor of long-term health and risk of chronic complications in diabetes. An equally potent risk factor for diabetes complications is loss-to-follow-up care. Thus, for paediatric patients, it becomes especially important both to intensify diabetes control and to provide positive clinical encounters that support diabetes education and encourage consistent follow-up care as soon as possible after the diagnosis of diabetes. Efforts to optimise glycemic control and ensure follow-up care, as children grow into teens and young adults, remain an ongoing challenge. In an effort to meet this challenge and as an adjunct to routine diabetes care and education, we introduced Child Life services into the ambulatory paediatric program at the Joslin Clinic in 2002. The Child Life program aims to reduce stress and anxiety and to promote positive health perceptions and behaviours for youth with diabetes. The Child Life team includes certified Child Life Specialists along with multi-disciplinary members of the paediatric diabetes team. The interventions coordinated by the Child Life staff include: therapeutic activities, procedural support, medical play, recreational play, and general family support. Child Life offers developmentally targeted services with teachable moments through activities such as ‘Hypoglycemia Bingo’ and ‘Gardening and Caring for Diabetes’ in which the child compares how to take care of a plant and how to take care of diabetes. Child Life services are available to all paediatric and adolescent patients at Joslin. We recorded all Child Life interventions over a one-year period. We also assessed satisfaction with Child Life programming by surveys mailed to parents. There were 3,167 interventions during 1,644 patient visits among 702 different youth with diabetes (54% female). Patients utilizing Child Life support were 9.7 ± 4.1 years of age (X ± SD) with diabetes duration of 2.5 ± 1.9 years. Twenty percent of patients were <6 years old, 61% were 6–12 years old, and 19% were 13 + years old. Many interventions (39%) involved therapeutic activities facilitated by the Child Life staff working in small groups of patients/siblings; 21% involved procedural support for blood sampling, injections, or catheter insertions; 19% included recre-
involved supervised medical play sessions; and 8% of interventions involved general family support, including helpful techniques for blood glucose monitoring or insulin administration. In addition, the Child Life and Paediatric team offer two major events annually, including a Halloween Party and Teddy Bear Clinic. Each activity provides education with multiple ‘teachable moments’ for youth, siblings, and parents. The Teddy Bear Clinic incorporates numerous stations in which the child administers diabetes care to his/her favourite doll or teddy bear. Families and youth have responded positively to Child Life services. Family survey responses revealed 94% satisfaction with Child Life activities and 85% satisfaction with laboratory/procedural support. The latter effort is especially important since phlebotomy tends to be particularly difficult for young children and families. In summary, Child Life services are widely accepted in our paediatric outpatient setting. Patients of both genders and of all age groups utilize these activities. Families report a high rate of satisfaction. The incorporation of Child Life services as a part of comprehensive diabetes medical care and education promotes positive experiences for the child and family living with diabetes and will likely enhance health outcomes. Consistency of follow-up care for patients exposed to Child Life services is likely to improve throughout childhood and into young adulthood due to the positive experiences and educational support received during these critically important developmental years.

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teaching skills with small groups. ii) To test and refine the course in terms of acceptability, educational content and teaching material. Interview of participants and parents gave user feedback. An independent educationalist observed two days of each course and reported on teaching methods, consistency of teaching and course materials.

Conclusions: The involvement of experienced teachers proved invaluable. Feedback was very positive and the educational curriculum produced appears to be acceptable and to meet independent educational standards. Delivering intensive education to groups of young people for several consecutive days requires new skills. Our model of educator training was thought to provide good preparation for teaching this course. It remains to be seen whether adolescents can improve and sustain their self management skills as a result of this course and whether it will have an impact on glycaemic control. ‘Top-up’ education appears to be required, particularly in an age group where motivation can be difficult to maintain. Delivering effective diabetes education is complex and time consuming and projects such as this raise more questions than they answer: Education should be based on assessment of need – how best to measure this? Does intensive teaching place too much of a burden on patients and health professionals or can the same be achieved by shorter sessions? Is group work more effective than individualised sessions? How to deliver effective education to children of different ages and differing intellectual and social backgrounds? Should all diabetes team members receive specific educator training? What models are most effective?