Diabetes Under Seven (DU7)

Aspects of glycaemic control, hypoglycaemia, nutrition and physical activity in children younger than seven years with type 1 diabetes mellitus

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Ineko

Blott den förtjänar makt som dagligen rättfärdigar den

Only they deserve power who daily justifies it

Dag Hammarskjöld

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Aspects of glycaemic control, hypoglycaemia, nutrition and physical activity in children younger than seven years with T1DM

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ABSTRACT

Aim: The aim of this thesis is to elucidate the specific challenges in insulin treatment for children younger than seven years with type 1 diabetes, with a focus on glycaemic control, hypoglycaemia, nutrition and physical activity.

Methods: There were 24 children younger than seven years with type 1 diabetes and 27 healthy children from Gothenburg in the observational study that forms the basis of this thesis. Continuous glucose monitors, glucometer memories, accelerometers, food diaries, logbooks and questionnaires were used to collect data on the everyday life of these children.

Results: In Paper I we showed that children with type 1 diabetes are less physically active than healthy children. In Paper II we found that most hypoglycaemic events in very young children with type 1 diabetes are asymptomatic and go undetected despite on average 10 plasma glucose tests per day. In Paper III we observed that both children with type 1 diabetes and healthy children eat too much saturated fat and too little fruit, vegetables and fibre. In Paper IV we found that young children with type 1 diabetes have lower health-related quality of life than healthy children of the same age and gender.

Conclusion: The circumstances and health-related quality of life of young children with type 1 diabetes need more attention from the health care system. Modern technical tools should be used to improve hypoglycaemia detection and to reduce glycaemic variability. These children's low physical activity and their food intake habits are associated with high cardiovascular risk and warrant further family-based support from the diabetes team.

Keywords: preschool children, type 1 diabetes, glycaemic control, hypoglycaemia, nutrition, physical activity, health-related quality of life

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SAMMANFATTNING

Omkring en tiondel av alla barn med diabetes i Sverige är yngre än sju år, dvs ca 800 barn i Sverige. Sjukdomen typ 1 diabetes innebär att kroppen inte kan bilda det livsnödvändiga hormonet insulin. Insulin tillförs istället antingen via insulinpump eller med injektioner flera gånger dagligen. Syftet med behandlingen är att bibehålla hälsa och livskvalitet på kort och lång sikt.

För högt blodsocker medför risk för komplikationssjukdomar, i första hand hjärt-kärlsjukdomar, ögonskador, njursjukdom och fotsår. För lågt blodsocker medför, förutom inlärnings- och koncentrationssvårigheter för stunden, risk för medvetslöshet och kramper. Blodsockret mäts många gånger per dygn för att styra behandlingen.

För att nå lagom blodsocker måste matintag, insulindoser och fysisk aktivitet balanseras mot varandra. För ett litet barn är det föräldrar och andra vuxna såsom förskolepersonal sam dagligen fattar alla dessa beslut i barnets egenvård.

Då typ 1 diabetes idag inte kan botas förväntas de barn som får diabetes under småbarnsåren ha diabetes under mycket lång tid. Den långa sjukdomstiden gör risken att drabbas av komplikationssjukdomar stor. För att minimera komplikationsrisken är det, utöver att normalisera blodsockret, viktigt att påverka andra riskfaktorer såsom kost och fysisk aktivitet. Detta är extra betydelsefullt då vanor etablerade under småbarnsåren tenderar att följa med under hela livet.

Denna studie visar att förskolebarn med diabetes är mindre fysiskt aktiva än friska jämnåriga. Barn med diabetes äter, liksom friska jämnåriga, för mycket mättat fett samt för lite frukt, grönsaker och fibrer. Detta medför en ökad risk för hjärt- kärlsjukdom och är oroande inför framtiden.

Studien visar att småbarn med diabetes har lägre livskvalitet än friska jämnåriga.

Studien visar att småbarn med diabetes har svängigt blodsocker och svårt att upptäcka låga blodsockervärden trots mycket intensiva insatser från föräldrar och andra vuxna och trots i genomsnitt tio blodsockerprover per dygn, ofta även på nätterna. Modern teknologi för kontinuerlig mätning av sockernivåer finns och bör vara tillgänglig, utvecklas vidare och anpassas för småbarn med diabetes då den kan förenkla vardagen för barn och föräldrar.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Sundberg F, Forsander G, Fasth A, Ekelund U. Children younger than 7 years with type 1 diabetes are less physically active than healthy controls. Acta Paediatrica 2012: 101; 1164-1169.

II. Sundberg F, Forsander G. Detection and treatment efficacy of hypoglycemic events in the everyday life of children younger than 7 yr. Pediatric Diabetes 2014: 15: 34–40.

III. Sundberg F, Augustsson M, Forsander G, Cederholm U, Axelsen M. Children under the age of seven with diabetes are increasing their cardiovascular risk by their food choices. Acta Paediatrica 2013 doi;10.1111/apa.12533

IV. Sundberg F, Sand P, Forsander G. Health-related quality of life and glycaemic control in pre-school children with diabetes. (Submitted).

CONTENTS

ABBREVIATIONS

ADA	American Diabetes Association
AGE	Advanced glycation end product
BMR	Basal metabolic rate
cpm	Counts per minute
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
E%	Energy percent
EDIC	Epidemiology of Diabetes Interventions and Complications
FIL	Food intake level
GH	Growth hormone
HAAF	Hypoglycaemia-associated autonomic failure
HRQOL	Health-related quality of life
ISO	International Organization for Standardization
ISPAD	International Society for Pediatric and Adolescent Diabetes
MDI	multiple daily injections
MVPA	Moderate and vigorous physical activity
NGSP	National Glycohemoglobin Standardization Program
PAL	Physical activity level

PUFA	Polyunsaturated fat
ROS	Reactive oxygen species
SAP	Sensor-augmented pump therapy
SMBG	Self-monitored plasma glucose
SUFA	Saturated fat
SWEDIABKIDS	the Swedish paediatric diabetes quality registry
T1DM	Type 1 diabetes mellitus
WHO/FAO	World Health Organization / UN Food and Agriculture Organization

1 INTRODUCTION

The prelude of this thesis was a concrete experience during my first years in paediatric training. One afternoon I was meeting a family in the emergency room. The parents had brought their two-year-old daughter to the hospital. She was suffering from classical symptoms of diabetes – polyuria and thirst – and her plasma glucose was around 30 mmol/l so the diagnosis was rather easy to make: type 1 diabetes mellitus (T1DM). Luckily, the lab results showed no signs of ketoacidosis and the girl looked quite well, playing in a corner of the emergency room.

Although the parents had suspected what the problem was, they were of course overwhelmed and shocked by the confirmation of the diagnosis. They had burning questions in that first meeting and over the following days: what will the future bring for her? Will she be able to live a good life? Will she be blind and crippled by the disease? What can we do to help her? And how can we manage this complicated treatment at home?

Good answers to these questions, based on research and clinical experience, are needed to provide useful strategies for families in this situation. Meeting the very young child with T1DM is a special challenge for the diabetes team. How can we bring insulin treatment into the everyday life of a very young person and her family? What care is needed to maximise the likelihood of a long and healthy life? And how do we, as members of the diabetes team, support a good current and future quality of life?

The incidence of T1DM is increasing among preschool children (Patterson) and, in Sweden, approximately 10% of children with T1DM are younger than seven years of age (SWEDIABKIDS).

Good glycaemic control from the early years of insulin treatment is known to reduce the risk of diabetes complications (Nathan). Paediatric treatment targets are defined in order to reach an acceptable risk reduction (Rewers). HbA1c is the gold standard for monitoring glycaemic control in epidemiological studies; however, HbA1c tests only indicate mean glycaemia, which overlooks other aspects of glycaemic control. The impact of early dysglycaemia in the young brain is a matter of particular concern (McCrimmon, Arbelaez).

Hypoglycaemia is a major problem in everyday life among children with T1DM, and the limiting factor when striving for normoglycaemia. Severe

hypoglycaemia causes seizures and loss of consciousness and can therefore be harmful and frightening. It can also impair long-term cognitive outcome (Åsvold). Severe hypoglycaemia is most often preceded by repeated episodes of mild hypoglycaemia (Cox 2007, JDRF 2011) which is known to interfere with cognition and learning (Gonder-Frederick 2009, Ryan 1990).

T1DM is associated with a tenfold increased risk of cardiovascular disease (Laing). Atherosclerosis starts early in life (Strong) and is more pronounced in persons with T1DM (Larsen). Endothelial dysfunction has been identified in early adolescence in children with T1DM (Järvisalo, Margeirsdottir, Trigona). Advances in the treatment of T1DM have resulted in a temporal decline in both mortality and microvascular complication rates, but similar declines in cardiovascular disease have not yet been observed (Pambianco).

Hyperglycaemia is a major risk factor for cardiovascular disease in people with diabetes (Lachin) but other risk factors are important as well. It is important to address other significant lifestyle factors, such as nutrition and physical activity, that have an impact on cardiovascular risk as early as possible. It is therefore recommended that children with T1DM restrict their intake of saturated fat and eat a diet rich in fibre, fruit and vegetables (Smart 2009). Less physical activity is associated with cardiovascular risk factors and early markers of atherosclerosis in older children with T1DM (Trigona). Habits established in childhood have a great propensity to continue into adulthood and thus affect both current and future risk accumulation (Kaikkonnen, Telama, Biddle).

The aim of insulin treatment in T1DM is to retain health and quality of life in the short and long term. Health-related quality of life (HRQOL) needs to be followed up as an integrated part of treatment evaluation in all children with T1DM (Delamater, Pihoker).

Most research in paediatric diabetology focuses on older children and adolescents with T1DM. Less is known about the situation of very young children with T1DM and the aim of this thesis is to add some information to this special area of paediatric diabetology. Such information would have been helpful when planning that girl's healthcare and providing her parents with good answers to their questions in the emergency room several years ago.

2 BACKGROUND

Diabetes mellitus is characterised by hyperglycaemia, defined as fasting plasma glucose ≥7.0 mmol/l or random plasma glucose ≥11.1 mmol/l (Craig). According to the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (JDRF CGM) study group, healthy children aged 8–15 years are in the glucose range 4.0–7.8 mmol/l for 93% of the time (JDRF 2010). T1DM is caused by a loss of insulin-producing pancreatic ß-cells. The result is relative insulin deficit that progresses to absolute insulin deficit, increased plasma glucose levels, intracellular starvation and ketonaemia. Untreated, the disease causes death from ketoacidosis. There is no effective cure available, and treatment consists of substituting insulin by subcutaneous injections or via continuous subcutaneous insulin infusion (CSII) with an insulin pump. The goal of the treatment is to mimic physiological insulin secretion and restore normal metabolism. Insulin affects the metabolism of all macronutrients (carbohydrates, protein and fat) and is necessary for normal growth. All these aspects need careful monitoring in diabetes care. The main focus in everyday insulin treatment is to achieve glycaemic control; this means a constant striving for normoglycaemia, i.e. to keep plasma glucose within the narrow physiological range.

2.1 The triad of dysglycaemia

Children with T1DM are exposed to all aspects of dysglycaemia (hyperglycaemia, hypoglycaemia and glycaemic variability) during insulin treatment. It is hard to study the outcome of each variable separately, since they all occur in the same individual; besides, the combination of different aspects of dysglycaemia could be more harmful than each component separately.

2.1.1 Hyperglycaemia

According to the JDRF CGM study group, healthy children aged 8–15 have glucose levels ≥7.8 mmol/l for 1.3% of the time (JDRF 2010). Hyperglycaemia causes microvascular and macrovascular diabetes complications (Martin, de Boer, Aiello, Lachin) and the mechanisms are glycosylation of proteins, oxidative stress and inflammation (Ceriello).

The cause of hyperglycaemia during insulin treatment is absolute or relative lack of insulin, often caused by a mismatch between insulin dose, carbohydrate intake and insulin sensitivity (which fluctuates in all

individuals). Under physiological conditions the ß-cell senses the glucose concentration and releases insulin immediately in a fast peak followed by a slow phase. Normally, insulin is drained in the portal circulation and a large proportion is extracted by the liver. Mimicking this by injecting or infusing insulin subcutaneously, based on active decisions by the insulin-treated child or the caregivers, is not easy and the result is often hyperglycaemia or hypoglycaemia.

Severe hyperglycaemia causes symptoms such as polyuria, thirst, tiredness and sometimes irritability, especially in young children. More pronounced lack of insulin causes ketoacidosis, a condition which, if untreated, is fatal. Mild hyperglycaemia is most often asymptomatic and will not be detected without monitoring.

2.1.2 Hypoglycaemia

Hypoglycaemia is defined as plasma glucose ≤3.9 mmol/l (Clarke, Seaquist). According to the JDRF CGM study group, healthy children aged 8–15 years have glucose levels ≤3.9 mmol/l for 2.0% of the time (JDRF 2010).

Hypoglycaemia in insulin treatment is the result of an imbalance between available glucose, insulin level and insulin sensitivity. It is often the limiting factor when striving for normoglycaemia in insulin treatment.

Counterregulation in healthy individuals

In healthy individuals, plasma glucose levels are physiologically maintained in a narrow range. Insulin secretion is reduced almost to nil when plasma glucose levels sink to just above 4.0 mmol/l. Normally, plasma glucose levels then stabilise at that level. As a secondary defence, glucagon is secreted from pancreatic α-cells and adrenalin is released from the sympathetic nervous system and adrenal medullae. Glucagon mobilises glycogen that is stored in the liver and increases ketogenesis. Adrenalin stimulates hepatic glycogenolysis and both hepatic and renal gluconeogenesis; it reduces glucose influx in muscular tissue and mobilises gluconeogenic precursors and fat to the liver. Adrenalin also suppresses insulin secretion. As a response to prolonged hypoglycaemia, growth hormone (GH) and cortisol are released. When plasma glucose rises, insulin is again instantly secreted from the pancreatic ß-cells (Cryer, Frier).

Counterregulation in insulin-treated children

Iatrogenic hypoglycaemia is caused by a relative overdose of insulin, too low carbohydrate ingestion, or higher carbohydrate demand or insulin sensitivity than expected as a result of physical activity. Due to the artificial situation in

insulin treatment, several of the physiological responses that maintain normoglycaemia are blunted.

Subcutaneously administered insulin has a slower mode of resorption and longer action than naturally secreted insulin. Once administered, an insulin dose cannot be removed; instead, the individual has to counterbalance the dose through active measures.

Several defects in hypoglycaemia counterregulation can be observed even in young children with T1DM (DirecNet 2009, Matyka). For unknown reasons, a decline in α-cell function is evident soon after diabetes diagnosis. The permissive signal for glucagon release is a rapid drop in insulin secretion, which does not occur in hypoglycaemia arising from subcutaneous insulin treatment (Cryer).

Blunted adrenergic response to hypoglycaemia deprives the child of the normal warning symptoms of hypoglycaemia, such as shaking and tachycardia. Thus, the first symptoms of hypoglycaemia can be neurocognitive, for example, confusion, stubbornness, fatigue or slow thinking. These symptoms can make it harder for the child to handle the situation correctly. In hypoglycaemia unawareness, adrenalin release in response to hypoglycaemia is reduced. Hypoglycaemia-associated autonomic failure (HAAF) is thought to be driven by repeated exposure to hypoglycaemia and can, at least partially, be reversed by freedom from hypoglycaemia for a period of some weeks (Cryer). Access to alternative fuels such as free fatty acids or ketone bodies is limited in hyperinsulinaemic hypoglycaemia, due to the physiological actions of insulin.

After a hypoglycaemic event, the child with T1DM, unlike the healthy child, lacks the automatic adjustment of insulin levels to balance the counterregulation. This phenomenon can, in combination with overtreatment with excessive carbohydrates, result in hyperglycaemia after hypoglycaemia.

Mild hypoglycaemia

Mild hypoglycaemia is a common adverse event in insulin treatment. The incidence is not well defined, partly because detection is difficult even in adults (Cox 2010) and older children (Gonder-Frederic 2008, DirecNet 2009). Mild hypoglycaemic events are defined as those that can be resolved independently by the affected person (in this case the child, with age-appropriate support from caregivers) (Clarke, Seaquist). Even mild hypoglycaemic events reduce cognitive capacity and learning (Ryan 1990, Gonder-Frederic 2009). In adults, this can increase the risk of accidents,

especially driving accidents (Cox 2010). Repeated mild hypoglycaemic events are associated with reduced warning symptoms of hypoglycaemia and an increased risk of severe hypoglycaemia (Cryer).

Severe hypoglycaemia

Severe hypoglycaemia in young children on insulin treatment is defined as seizures and coma caused by low plasma glucose (Clarke, Seaquist). The incidence of severe hypoglycaemia in insulin-treated children is reported to be 8–30 events per hundred patient years (Clarke). Concern has been raised that severe hypoglycaemia events can be at least partly responsible for the negative cognitive consequences seen in early-onset diabetes (Åsvold).

Fear of hypoglycaemia

Hypoglycaemia can be unpleasant and frightening. Fear of hypoglycaemia can induce problem behaviours such as overeating, underdosing of insulin and limiting physical activity in adults with T1DM (Anderbro, Brazeau). Fear of hypoglycaemia among parents of young children with T1DM is common (Patton 2008) and it has been shown to be associated with higher HbA1c in their children (Haugstvedt). Fear of hypoglycaemia in the child or parent is associated with lower health-related quality of life (HRQOL) for the child (Johnsson) and higher parental emotional distress (Patton 2008, Haugstvedt).

2.1.3 Glycaemic variability

It is suspected that glycaemic variability contributes to the risk of diabetes complications beyond the simple effect of elevating mean glycaemia, as measured by HbA1c. Transient hyperglycaemia has been shown to induce persistent epigenetic changes both in cultured human aortic cells and in healthy mice (El-Osta), thus providing a possible molecular explanation for the the contribution of glycaemic variability to the risk of diabetes complications.

According to the JDRF CGM study group, glycaemic variability, measured as SD of self-monitored plasma glucose (SMBG) or of CGM, in healthy children aged 8–15 years is <1 mmol/l (0.91 mmol/l (JDRF 2010). A suggested target in insulin treatment is that SD of plasma glucose should be less than 1/3 of mean plasma glucose, but a more realistic target would be less than 1/2 of mean plasma glucose (Hirsch). If target mean plasma glucose is in the upper limit of the physiological range (7 mmol/l), this would mean that a realistic target SD of plasma glucose in insulin treatment would be <3.5 mmol/l.

A study of C-peptide-positive children and adolescents (aged 8–18 years) with newly diagnosed T1DM found that their SD of mean CGM glucose was 2.5 mmol/l, compared to a group of C-peptide-negative children and adolescents matched for age and HbA1c, whose SD of mean CGM glucose was 3.6 mmol/l (Sherr).

SD is often used as a measurement of glycaemic variability. However, this measure has been criticised for being primarily dependent on hyperglycaemic excursions and for being relatively insensitive to hypoglycaemia. This is due to the asymmetry of the plasma glucose scale, with target values 4–7 mmol/l (Kovatchev). There is no consensus on the most appropriate measurement, and several different methods have been suggested, focusing on different aspects of glycaemic variability, with none of them obviously superior to the others.

2.2 Long-term complications of early-onset T1DM

The acute consequence of absence of insulin is death by ketoacidosis. Lack of insulin is globally the leading cause of death among children and adolescents with T1DM (Daneman 2009). Long-term survival only became possible after the introduction of subcutaneous insulin treatment in 1922.

Many, but not all, long-term survivors on insulin treatment have acquired diabetes complications, usually classified as macrovascular (myocardial infarction and stroke) and microvascular (renal disease, retinopathy and peripheral neuropathy).

The main risk factor for microvascular complications is hyperglycaemia, as evidenced by elevated HbA1c. Good glycaemic control from the early years of insulin treatment substantially reduces the risk of severe diabetes complications and cardiovascular disease (Nathan).

Besides poor glycaemic control, other important risk factors for microvascular and macrovascular complications are genetic susceptibility, gender, smoking, low physical activity, food choices and overweight or obesity (Donaghue 2009).

In addition, evidence is accumulating for cerebral complications as a third class of diabetes complications (McCrimmon, Arbelaez).

2.2.1 Microvascular complications of early-onset T1DM

The youngest participants in the DCCT/EDIC study were 13 years old at inclusion. (There were 195 adolescents aged 13–17 years.) Microvascular complications of diabetes are extremely rare before puberty, and it was previously argued that the development of these complications is unrelated to pre-pubertal diabetes duration (Donaghue 2003, Hamnes, Donaghue 2009).

The current theory is that the pathophysiological process of microvascular complications starts early in children with T1DM and accelerates during puberty (Marcovecchio, Daneman 2005, Cho), when the first detectable signs of microangiopathy become overt. An increase in advanced glycation end products (AGEs) resulting from the protein glycosylation that is thought to precede complications has been described in prepubertal children with T1DM (Berg). There is a strong association between a child's HbA1c level as early as 3–15 months after diagnosis and HbA1c level and complication status in adulthood (Samuelsson).

Data from the national Swedish paediatric childhood diabetes quality registry SWEDIABKIDS show that 9909 fundus photographs have been performed as routine screening for retinopathy in children and adolescents with T1DM living in Sweden during the period 2008–2012.The frequency of retinopathy (almost exclusively simplex retinopathy) increased gradually with longer diabetes duration, from 4.9% in children and adolescents with 0–4 years diabetes duration, to 12% in children and adolescents with 5–9 years diabetes duration and 30% in children and adolescents with 10–15 years of diabetes duration (SWEDIABKIDS annual report 2012). Retinopathy screening is performed biennially in all children with T1DM in Sweden from the age of ten years, and yearly if retinopathy is detected. The oldest children in the report are 17.9 years old; this means that the children in the group with the longest diabetes duration and highest frequency of retinopathy were all diagnosed with T1DM before the age of eight years. This suggests that prepubertal diabetes duration affects the risk of retinopathy.

2.2.2 Macrovascular complications of early-onset T1DM

Cardiovascular disease, such as myocardial infarction and stroke, is the leading cause of death in people with diabetes as well as in the general population (Lachin). Atherosclerosis causing cardiovascular disease starts early in life (Strong) and this process is more pronounced in children with

T1DM than in healthy children (Järvisaalo, Larsen, Margeirsdottir). Diabetes is associated with a tenfold increase in the risk of cardiovascular disease (Laing) and this risk has not been reduced over time, despite a reduced risk of microvascular complications through improved glycaemic control (Pambianco). Women with diabetes in particular have a hugely increased risk of cardiovascular disease compared to healthy women (Laing).

There is an association between early signs of atherosclerosis (such as intima media thickness) and age at onset of T1DM, with a higher risk for the children who were youngest at diagnosis (Margeirsdottir). Higher HbA1c over a long period is associated with more pronounced signs of atherosclerosis (Larsen, Lachin). A higher level of physical activity is associated with less pronounced signs of atherosclerosis in children with T1DM (Trigona).

2.2.3 Cerebral complications of early-onset T1DM

There is growing evidence that children with T1DM are at risk of developing cognitive difficulties. A meta-analysis showed that the risk is largest for children with early-onset diabetes and that the effect is already detectable after a mean diabetes duration of six years. The effect size is moderate but large enough to affect school performance (Gaudieri). According to Gaudieri, the effect size was largest on learning and memory (0.49 SD lower than healthy children of the same age) but observable on all testing domains.

The brain's energy demand has reached adult levels at the age of two years and is nearly twice the adult rate by the age of 10 years. The brain is almost exclusively dependent on glucose as its energy source in physiological conditions. Thus, the brain consumes a high proportion of the child's circulating glucose. Glucose uptake by the brain is insulin-independent and mainly driven by the concentration of glucose. This directly exposes the neuronal cells of the brain to oxidative stress and glucotoxicity in hyperglycaemia and to lack of fuel in hypoglycaemia. The maturation of grey matter in the brain is intense until the age of six years, while the evolution of white matter continues until early adulthood. During these periods the brain is sensitive to metabolic disturbances, and areas of concern have repeatedly been identified in MRI studies of young brains exposed to glycaemic extremes, as in T1DM (Arbelaez).

The mechanisms of brain damage in T1DM are not clearly understood. Hyperglycaemia (Hannonen) as well as hypoglycaemia (especially with seizures) (Åsvold) and oxidative stress caused by glycaemic variability

(McCrimmon) have been implicated. The main effects seem to occur in the early phase of the disease and it has been suggested that metabolic conditions such as hyperglycaemia and sometimes ketoacidosis around diagnosis can be a predisposing event that makes the brain more sensitive to further glycaemic events and periods of dysglycaemia (McCrimmon, Ryan 2008). Animal models have been used to explore the issue and hyperglycaemia has been shown to induce histological changes in young rat brains (Malone).

2.3 Glycaemic memory

In the Diabetes Control and Complications Trial (DCCT), 1441 subjects with T1DM were were randomly assigned to intensive or conventional insulin treatment. Intensive treatment consisted of three or more insulin doses per day, either as multiple daily injections (MDI) or with an insulin pump monitored by SMBG at least four times per day, as well as access to extra support from the health care system. Conventional insulin treatment at the time of the study (the early 1980s) was one or two daily insulin injections. The patients in the intensively treated group achieved a lowered HbA1c of 7.2% NGSP (55 mmol/mol), whereas the conventionally treated patients had an average HbA1c of 9.1% (76 mmol/mol) during the six-year study period. The risk of microvascular diabetes complications was reduced dramatically in the intensively treated group by the end of the relatively short study period.

After the study, all patients were offered the same kind of intensive treatment but with less support than during the study period. Both groups went on to have the same mean HbA1c (8.0% NGSP = 64 mmol/mol).

The Epidemiology of Diabetes Interventions and Complications Study (EDIC) followed up the DCCT intervention and showed that the difference in incidence of diabetes complications continued to increase between the two different treatment groups during the first four years of follow-up. This effect has been shown to last ten years and has been named “metabolic memory” (Nathan).

It has been shown that HbA1c values from the previous two to three years contribute most to the current risk of retinopathy developing or worsening. HbA1c values from up to the previous five years contribute more than current values and values from up to the previous eight years still have important impact on current risk of retinopathy (Lind).

The mechanisms of the metabolic memory are currently being investigated. In 1999 the DCCT Skin Collagen Ancillary Study Group reported data regarding glycosylation of collagen in a study of skin biopsies in DCCT participants. They found that these long-lasting AGEs were more abundant in individuals with microvascular complications and on conventional insulin treatment than in intensively treated patients (Monnier). The increased formation of AGEs has later been attributed to increased formation of reactive oxygen species (ROS) by the mitochondrial electron transport chain as a result of hyperglycaemia. Apart from activating processes leading to vasculatory inflammation this also causes persistent epigenetic changes (Ceriello). It has been suggested that the presence of ROS initiates methylations of histones affecting transcription and thus mediates hyperglycaemia-induced changes in gene expression that persist despite a return to normal glucose levels (Keating).

2.4 Monitoring glycaemic control

2.4.1 HbA1c

Glucose can freely enter erythrocytes and binds covalently to the ß-chain of haemoglobin A (α2ß2) forming HbA1c. The process is nonenzymatic and driven by the concentration of glucose. The proportion of HbA1c to HbA (measured in mmol/mol or percent) thus reflects mean glycaemia during the 120-day lifespan of the erythrocyte (Bunn). Clinically, HbA1c mainly reflects glycaemic control during the preceding 6–8 weeks and at least four measurements per year are recommended (Rewers).

HbA1c was used to investigate the importance of glycaemic control in the DCCT/EDIC study (Nathan). It was shown that HbA1c as a marker of glycaemic control is strongly associated with the risk of diabetes complications. No safe level indicating null risk of diabetes complications could be identified, but the risk reduction by lowering HbA1c was greatest in the groups with the highest HbA1c.

HbA1c is used to monitor overall glycaemic control in individuals. The advantage is that HbA1c reflects all times of the day and week, regardless of activities such as sleep or active glucose monitoring by the individual. HbA1c reflects glycosylation and the individual's risk for microvascular and macrovascular complications of diabetes.

It is also used (in combination with other measurements) to monitor the quality of diabetes care at different centres.

2.4.2 Self-monitoring of plasma glucose values (SMBG)

Self-monitoring of plasma glucose values in everyday life was introduced as a cornerstone of insulin treatment in the 1980s. The technical equipment for performing capillary testing, analysing results and storing and interpreting data has evolved continuously since then. The precision of the meters is today systematically reviewed, and a precision of 15% (or ±0.83 mmol/l if plasma glucose is <5.6 mmol/l) is now judged as acceptable according to ISO standard 15197:2013. A higher plasma glucose testing frequency – up to five values per day – has been shown to be associated with lower HbA1c levels (Ziegler). Children and adolescents using SMBG are recommended to test plasma glucose values 4–6 times per day (Rewers).

SMBG gives the child and caregivers immediate feedback on treatment decisions and provides the information necessary to make the next decision regarding insulin dosing and food intake. Data from glucometers can be uploaded into a computer and used retrospectively for analysis of glycaemic control. The disadvantages are, first, that it gives a snapshot of the current situation but says nothing about the plasma glucose levels between testing points and, second, that the child and the caregivers have to interrupt other activities to focus on the testing and perform a finger prick whenever they need information about the child's glucose level.

2.4.3 Subcutaneous continuous glucose monitoring (CGM)

Approximately 20 years after the introduction of SMBG, the technique of subcutaneous CGM appeared. The first device was approved by the US Food and Drug Administration (FDA) in 1998. The first device collected glucose values over three days; the data were transferred to a receiver through a cable and could then be uploaded to a computer and analysed afterwards by the diabetes team and patient (known as "blinded CGM"). The technical equipment for subcutaneous CGM is still evolving. Today's CGM is wireless and provides direct information regarding current glucose levels ("real-time CGM") (Cunningham).

The real-time CGM monitor presents the current glucose level with a figure, a graph and an arrow indicating the direction of the change of glucose level. Different colours can be used to indicate hyperglycaemia, hypoglycaemia and normoglycaemia. The system can be customised by the user to give alarms at chosen glucose levels, or when glucose levels change rapidly or when

hypoglycaemia is imminent. When integrating an insulin pump and CGM, it is possible to program the pump to stop delivering insulin for two hours as a rescue response to hypoglycaemia undetected by the user.

Glucose data can be presented either on the screen of an insulin pump or on a separate monitor. It is possible to show data from one CGM on two separate monitors, allowing the caregivers to watch the child's glucose level from a distance without interrupting the child's ongoing activities, such as playing.

The precision of the best CGM systems available today is comparable with the precision of SMBG, although no ISO standards exist. CGM can be used by toddlers (Tsalikian) from the onset of T1DM (Kordonouri 2010), though usability improvements will be necessary to increase the use of the technology (Tsalikian, Kordonouri 2010). When used frequently (more than 80% of time), CGM contributes to lower HbA1c (Slover, Güttler) without increasing the frequency of hypoglycaemic events (Slover).When it is used frequently from the onset of insulin treatment, the decline in C-peptide has been reduced in children using a sensor-augmented pump (SAP) compared to patients with SMBG-guided pump treatment when measured two years after diagnosis (Kordonouri 2012).

CGM gives the child and caregivers immediate feedback on treatment decisions and provides the information necessary to make the next decision regarding insulin dosing and food intake. It also gives information on the direction of change in glucose levels and shows the glucose levels during the preceding 24 hours. Data from real-time or blinded CGM can be uploaded into a computer and used retrospectively for analysis of glycaemic control. Blinded CGM has become a useful tool in glycaemia research. The disadvantages of the technique are the cost and the need to insert the glucose sensor, a procedure that can be perceived as painful by the child. Young children have sensitive skin and the device can cause skin irritation and associated pain.

2.5 Lifestyle factors affecting cardiovascular risk

The American Heart Association (AHA) has identified certain childhood conditions associated with extremely high risk of cardiovascular disease, calling for treatments to minimise this risk. The list of conditions judged to be associated with this extremely high risk of cardiovascular disease includes homozygous familial hypercholesterolemia, T1DM, chronic kidney disease

or end-stage renal disease, post heart transplantation and Kawasaki's disease with current aneurysm. For a disease to be on this list, there has to be pathological or clinical evidence for manifest coronary disease before 30 years of age. The AHA categorises these diseases as a *coronary heart disease equivalent*, with recommendations similar to the secondary prevention guidelines for adults with established coronary disease. The AHA recommends that risk factors such as growth, nutrition, blood lipids, blood pressure, smoking and physical activity should be carefully monitored and treated (Kavey). Of these risk factors, nutrition and physical activity are the most relevant in the preschool years.

Lifestyle habits, such as nutritional preferences (Kaikkonnen), physical activity (Telama) and time spent sedentary (Biddle), that are established in childhood have a great propensity to follow into adulthood. Thus, lifestyle factors in early childhood have a dual impact on later cardiovascular risk, observable both as early markers of atherosclerosis during adolescence (Trigona) and also as a set of behaviours that increases or reduces the person's risk of cardiovascular disease as an adult and even into senescence.

2.5.1 Nutrition

Several aspects of nutrition affect glycaemic control and thus the risk for long-term complications of diabetes.

All macronutrients (fat, protein and carbohydrates) affect the need for insulin (Woolperth, Smart 2013). In everyday practice, the estimation of the required amount of insulin is commonly made from carbohydrate content in food (Smart 2009). Attempts have been made to include quantification of other macronutrients in the estimation of insulin needed at meals (Pankowska, Kordonouri 2012). The discussion of the necessity and usefulness of this is currently ongoing (ISPAD 2013 annual meeting).

Other aspects of nutrition, such as skipping of meals (Øverby) and parental mealtime stress concerning the child's eating (Patton 2009), are associated with higher HbA1c.

Beside the factors directly associated with immediate glycaemic control, food choices have a great impact on the risk of cardiovascular disease in the long term. It has been shown that a high intake of fruit and vegetables is associated with less risk of cardiovascular disease (Mann). The same is shown for a high intake of fibre (Schoenacker). The recommendation for all children is to eat at least 400 grams of fruits and vegetables daily (Mann).

High intake of saturated fat is associated with increased risk of cardiovascular disease (Skeaff). Current recommendations for children with T1DM (as for all children) are that less than 10% of energy intake should consist of saturated fat (Uuay, Smart 2009). A healthy ratio of saturated to unsaturated fat intake is considered to be about 1 to 3 (Kromhout). Some practical advice from the Swedish Food Agency (www.slv.se visited 10 January 2014) is that all children should consume low-fat milk (less than 0.7g fat per litre) daily and oil-based spreads containing less than 41% fat, of which no more than one third is saturated, instead of high-fat spreads.

2.5.2 Physical activity

Physical activity confers many health benefits on healthy children. A strong graded inverse cross-sectional association has been observed between physical activity and insulin resistance (Brage, Andersen) and body fat (Steele). Spending more time in moderate and vigorous physical activity (MVPA) is associated with better outcomes on cardiometabolic risk factors, although time spent sedentary might have less impact in children (Ekelund).

Self-reported regular physical activity may be associated with lower HbA1c in children with T1DM (Herbst 2006); however, these results are equivocal (Åman). Physical activity can rapidly lower plasma glucose levels, which is usually beneficial but might also cause acute hypoglycaemia (Robertson). A lower level of physical activity is associated with other cardiovascular risk factors (Herbst 2007) and early markers of atherosclerosis (Trigona) in older children with T1DM.

It is hard even for parents of healthy children to estimate whether their child is sufficiently physically active (Corder 2010). Children with T1DM are often reported by their parents (and report themselves) to be just as physically active as healthy children (Heilman, Fereday) but, when measured objectively, they are shown to be less physically active than their healthy peers (Heilman).

2.6 Health-related quality of life (HRQOL)

The philosophical question of what quality of life is and how it can be achieved has been discussed since ancient times. Many factors can contribute to a high quality of life, for example, standard of living (access to food and drinkable water), sociological factors (participation in society, relations to family and others), psychological factors (self-esteem, decision-making, happiness) and medical factors. HRQOL is intended to be an integrated measurement of all the above-mentioned aspects of quality of life (Eiser).

HRQOL can be measured in the general population (generic HRQOL) or in a disease-specific group. Measuring generic HRQOL in a group with a specific disease enables comparison with HRQOL in the general population, while disease-specific HRQOL can be measured as a part of the evaluation of a treatment. For T1DM, the recommendation is to evaluate and monitor HRQOL as an integrated part of treatment outcome (Delamater, Pihoker).

Evaluating HRQOL in young children is a challenge. Children from the age of five years (sometimes with reading assistance) can usually answer questionnaires to give their own view of their HRQOL, but the questionnaire is often completed by a parent as the child's proxy. For children younger than five years, only proxy report by a parent can be used. Several different instruments exist, both generic and disease-specific for different conditions, but few of them are adapted for children younger than 6–8 years (Eiser).

In older children and adolescents with T1DM, high HRQOL is often associated with lower HbA1c (Hoey, Hassan). Adolescents with T1DM rate their own HRQOL higher than their parents rate the HRQOL of their teenager (Sand). Fear of hypoglycaemia, but not hypoglycaemia in itself, is associated with lower HRQOL in children and adolescents with T1DM (Johnsson). Better socioeconomic standard is associated with higher HRQOL in older children and adolescents with T1DM (Hassan). In a recent Norwegian study, there was no difference in HRQOL according to insulin delivery mode (pump vs injections) (Frøisland).

The information on HRQOL in preschool children with T1DM is scarce. Either the information is not collected or data are pooled with older children rather than reported separately.

2.7 Social consequences of early-onset T1DM

Early-onset diabetes is associated with lower school marks than in the general population, in both theoretical subjects and sports. A Swedish study found the largest difference in children who developed T1DM before the age of five years (Persson). When followed up at age 29, these individuals were employed to a lesser degree and earned less money than the general population in Sweden (Persson). The children in the Persson follow-up study were born in 1972–1977 and were diagnosed with T1DM in the years

preceding DCCT and the major switch to intensive insulin treatment in the beginning of the 1980s. During their childhood and adolescence, they benefitted from the technical and practical improvements of SMBG and insulin delivery.

Whether the adverse effects of early-onset diabetes on schooling and work mainly depend on the disease itself (hyperglycaemia), treatment (time-consuming procedures, psychological burden, treatment-related school absence, iatrogenic hypoglycaemia and glycaemic variability) or social expectations (from school, family or the child) is not fully understood.

3 AIM

The aim of this thesis is to elucidate the specific challenges in insulin treatment for children younger than seven years with T1DM, with a focus on glycaemic control, hypoglycaemia, nutrition and physical activity.

3.1 Hypotheses

3.1.1 Glycaemic control

Hypothesis 1: Preschool children with T1DM have good glycaemic control according to HbA1c results, but the proportion of time spent within the blood glucose target range is not satisfactory.

3.1.2 Hypoglycaemia

Hypothesis 2: Both over- and under-treatment of real or suspected hypoglycaemias contributes to fluctuating plasma glucose levels.

3.1.3 Physical activity

Hypothesis 3: Preschool children with T1DM are less physically active than healthy children of the same age and gender.

Hypothesis 4: Fear of hypoglycaemia is associated with less physical activity

3.1.4 Nutrition

Hypothesis 5: On average, preschool children with T1DM have the same intake of energy and macronutrients as healthy children of the same age and gender.

Hypothesis 6: Increased day-to-day variability in energy intake is associated with poorer glycaemic control, measured as both HbA1c and time spent within the plasma glucose target range.

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4 SUBJECTS AND METHODS

4.1 Study design

Design

All children who met the inclusion criteria (see below) were invited to participate in this study. The Diabetes Unit at the Queen Silvia Children's Hospital serves all children younger than 18 years with T1DM in the Swedish city of Gothenburg and its surrounding area

Each child was followed for one year (Figure 1). Data regarding height, weight, health and medication, socioeconomic situation and HRQOL were collected for all participants (children with T1DM and healthy control children) at inclusion. For the children with T1DM, all HbA1c values, height and weight measurements and data regarding severe hypoglycaemia events were collected prospectively during the year.

At inclusion, parents of the children with T1DM reported their child's current insulin treatment and history of severe hypoglycaemia, and the child's HbA1c was measured. They were provided with equipment for uploading the child's plasma glucose values in their homes and were encouraged to do so biweekly for one year. As a backup, the child's glucometer was uploaded at every scheduled visit to the diabetes clinic.

More detailed data regarding physical activity and nutrition were collected for all children during one week in autumn and one week in spring. During the same week, the children with T1DM also underwent CGM, and all detected and treated hypoglycaemic events, as well as all monitored plasma glucose values and insulin doses they had received, were reported in a diary.

Location

The city of Gothenburg has 520 000 inhabitants of whom 45 000 children are younger than seven years. The extended area (greater Gothenburg) has approximately 70 000 inhabitants younger than seven years. Of the inhabitants in the city of Gothenburg, 23% are immigrants. Of the inhabitants aged 25–54 years, 51% have had more than twelve years of education. In the population aged 20–64 years, 72% of men and 70% of women are employed, and of the population aged 18–64 years, 4% are unemployed (www.goteborg.se, visited 27 January 2014). Of Swedish

children aged 1–5 years, 83% (and 94% of those aged 4–5 years) attend day care centres (www.skolverket.se, visited 27 January 2014).

Gothenburg is located on the west coast of Sweden. In 2009, Gothenburg reported 171 days of precipitation (rain or snow). The mean temperature was -0.7˚C in February and 18.3˚C in July, and the mean temperature for the year was 8.8˚C. (www.goteborg.se, visited 27 January 2014). The sun is above the horizon approximately 6.5 hours per day during the darkest part of the year (December to January) and approximately 17.5 hours during the lightest part of the year (June–July).

4.2 Subjects

4.2.1 Children with T1DM

The Diabetes Unit at the Queen Silvia Children´s Hospital serves all children with T1DM in the Swedish city of Gothenburg and its surrounding area. A total of 53 children with T1DM met the inclusion criteria for this study and the parents of 24 of them (12 girls) consented to their child's participation in the study. The children were included if they were under seven years of age and had had T1DM for more than three months when they entered the study. The following exclusion criteria were applied: having another relevant disease (N=1), diagnosis of diabetes other than T1DM (N=3), insufficient knowledge of the Swedish language (N=0) and severe social deprivation (N=0). Four of the children with T1DM had well-regulated asymptomatic celiac disease diagnosed during screening and were not excluded. The children were recruited in 2008 and 2009.

The parents of 29 children with T1DM (13 girls) declined to participate in the study. Descriptive data regarding these children were collected from patient records. No significant differences were observed between participating and non-participating children in terms of mean age, mean diabetes duration or mean HbA1c. The only significant differences between the participating and non-participating children with T1DM were a higher proportion of children treated with insulin pump (17 of 24 vs 15 of 29) ($p<0.05$) among participants.

4.2.2 Healthy control children

The first step was to invite two healthy children of the same gender and age, from the same day care centre as the study child, to participate in the control group. Only nine healthy children from 8 of the 24 day care centres with participating children with T1DM could be recruited in this way. Children similar in age and gender distribution from two additional day care centres in different parts of Gothenburg were therefore invited and 18 additional healthy children were recruited. Thus, the children in the final control group were recruited from 10 different day care centres from the city of Gothenburg and surrounding areas. The inclusion criterion for the control group was that they had to be below seven years of age. The exclusion criteria were (1) any disease that significantly affected their food intake or physical activity and (2) an inability to understand Swedish. One parent of each child in the control group was interviewed about their child's health.

4.2.3 Data from the SWEDIABKIDS registry

National data describing all children in Sweden who had had diabetes mellitus for more than three months and who were younger than seven years of age on 1 November 2008 were retrieved in December 2013 from the Swedish paediatric diabetes quality registry, SWEDIABKIDS.

4.3 Measurements

4.3.1 HbA1c

HbA1c was measured with DCA Vantage (Siemens Healthcare Diagnostics Inc., Tarrytown NY, USA) with a normal value of 27–42 mmol/mol, quality assured in accordance with Equalis (External quality assurance in laboratory medicine in Sweden, www.equalis.se).

4.3.2 Plasma glucose values

Plasma glucose was measured with the child's ordinary glucometer. Sixteen children used Freestyle Lite (Abbot Diabetes Care Inc., Alameda, USA),

seven used Contour (Bayer Consumer Care AG, Basel, Switzerland) and one child used both. The meter memory was uploaded via the computer software Diasend® (Diasend, Gothenburg, Sweden) repeatedly during the entire study year and noted in a logbook during one week in autumn and one week in spring.

Glucose strips are free for all patients with insulin-treated diabetes mellitus in Sweden, through reimbursement by the health service. Families were instructed to follow their normal routines for measuring the child's plasma glucose and to note the values in the study logbook during one week in autumn and one week in spring. During the rest of the year, plasma glucose values were collected by uploading glucometer memories at home and, as a backup, at the clinic.

4.3.3 Continuous glucose monitoring

CGM was performed with CGMS Gold (Medtronic MiniMed, Northridge, CA, USA). After application of topical anaesthetic (EMLA Cream, Astra Pharmaceuticals, Wayne, PA, USA), the subcutaneous CGM sensor was inserted in the child's abdomen or buttocks. Insertion was performed at the diabetes unit by trained personnel. Parents were instructed on the use and calibration of the CGM device according to the guidelines outlined by the manufacturer. The results of the registration were blinded to the study participant and the diabetes team for the entire study year. CGM data were analysed with the MiniMed Solutions CGMS Sensor 3.0 software. Hypoglycaemic events were identified by manual reading of the records and analysed. All periods fulfilling the definition of hypoglycaemia (glucose value $\leq$3.9 mmol/l) were used in the analysis.

4.3.4 Height and weight

Height and weight in all children were measured by a trained nurse from the diabetes unit. Height was measured to the nearest 0.1 cm with a stadiometer, with the child in standing position. Weight was measured to the nearest 0.1 kg on a calibrated electronic scale, with the child dressed in light clothing. The Body Mass Index Standard Deviation Score (BMI SDS) was calculated and compared with Swedish national growth charts.

4.3.5 Physical activity

Physical activity was measured using a combined movement and heart rate sensor, the Actiheart (Cambridge Neurotechnology, Cambridge, UK). The monitor was worn for one week during two different periods within 12 months (October–December and February–May) to account for potential seasonal variations. The Actiheart is lightweight (8 grams) and has been validated as an accurate tool for the assessment of physical activity in children (Corder 2008). It was attached to the chest using two standard ECG electrodes and was used continuously for seven consecutive days, including during sleep and water-based activities. Data were collected in 60-second epochs. Data were cleaned, and reported sick days were excluded before analysis. As part of the data reduction process, runs of continuous zeros ≥100 minutes were excluded. The methods for interpreting the combined heart rate and movement data are still being developed for this age group (Ulf Ekelund, personal communication); therefore, only the accelerometer data were used in this study, analysed using a custom-designed program (MAHUffe). Derived physical activity variables included daily activity counts (counts per minute, cpm) as an indicator of total physical activity and the time (minutes per day) spent at different intensity categories of physical activity (i.e. sedentary, light, moderate and vigorous). Cut-off points for time spent sedentary and in MVPA were estimated in advance using a laboratory protocol in which the volunteer simultaneously wore an Actigraph 7164 accelerometer and a combined movement and heart rate sensor while walking and running on a treadmill (Corder 2008). Sedentary was defined as less than 20 cpm, and moderate intensity physical activity as more than 400 cpm. These thresholds are broadly equal to 100 cpm and 2000 cpm, as obtained by the commonly used Actigraph accelerometer (Ridgeway).

4.3.6 Food record

Food intake was assessed by two repeated four-day food records from Saturday to Tuesday, once during the autumn and once during the spring within one year. The parents recorded food intake at home. At the day care centres, the staff recorded food intake with help from a dietician or research nurse. They were all equipped with digital kitchen scales and a measuring kit. The food records were analysed using a software programme (Dietist XP) based on the Swedish food database provided by the Swedish National Food Administration. Reported days with gastroenteritis (nine days in total for three children) were excluded before analysis.

Energy intake was determined individually from the food records. To identify under-reporting of energy intake at the group level for children with T1DM versus healthy children, the Goldberg cut-off method (FIL/PAL) was used. Food intake level (FIL) was calculated by dividing energy intake by basal metabolic rate according to tables by Black. Physical activity level (PAL) was estimated on a group level separately for boys and girls according to tables by Black. The PAL for one- to six-year-old boys was thus set at 1.64 and at 1.57 for girls with regard to gender and age (Black).

4.3.7 Hypoglycaemia diary

Families noted plasma glucose values, symptoms and treatment of hypoglycaemia during one week in autumn and one week in spring in a logbook specially designed for the project. Families were asked to do this concurrently with blinded CGM.

4.3.8 Health-related quality of life

The Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL 4.0) measure HRQOL and consist of self-report (child) and proxy-report (parent) scales (Varni 2001). The PedsQL 3.0 measures diabetes-specific HRQOL and is designed to be integrated with the PedsQL 4.0 generic measure (Varni 2003). The PedsQL 4.0 consists of 23 items in four scales: (i) physical functioning (eight items); (ii) emotional functioning (five items); (iii) social functioning (five items) and (iv) school functioning (five items, or three items in age group 2–4 years). The PedsQL 3.0 diabetes module consists of 28 items in five scales: (i) diabetes symptoms (11 items); (ii) treatment barriers (four items); (iii) treatment adherence (seven items); (iv) worry (three items) and (v) communication (three items).

Both the PedsQL 4.0 and the PedsQL 3.0 have been validated in the Swedish language (Petersen, Sand).

Both questionnaires are designed for children aged 2–18 years (2–4, 5–7, 8–12, 13–18 years), but for 2–4 year olds, only parent reports are included. The PedsQL 4.0 and PedsQL 3.0 both use a 5-point Likert scale (ranging from 0 = *never* to 4 = *almost always*) for all versions, except for the child report at 5–7 years, which uses a 3-point Likert scale (0 = *not at all*, 2 = *sometimes*, 4 = *a lot*). The items are reverse scored and transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), that is, higher scores indicate better HRQOL (Varni 2001). The PedsQL 4.0 and PedsQL 3.0 were administered at the clinic in the

case of the children with T1DM. The healthy children and their parents completed the PedsQL 4.0 only, either at the diabetes clinic or at the child's day care centre. In order to ensure that parent and child filled in the questionnaires separately, a trained nurse assisted the children. Either the mother or the father reported their child's HRQOL by completing the parent report.

4.3.9 Demographics

Parents were asked to supply information on their education level, whether the child was living with two cohabiting biological parents and whether the child and parents were born in Sweden.

4.4 Ethics

The study was performed in accordance with the Helsinki Declaration and was approved by the Regional Ethical Board of Western Sweden. Since the children were very young, all parents of the participating children provided written informed consent. The children were verbally informed about the study.

4.5 Definitions

Hypoglycaemia was defined in accordance with ISPAD and ADA as plasma glucose (or CGM glucose) ≤3.9mmol/l (Clarke, Seaquist).

Night-time was defined as 22:00–06:00.

4.6 Statistics

All statistical analyses were performed using SPSS 19 (SPSS Inc., Chicago, IL, USA). Differences were considered significant at $p<0.05$.

Paper I

Differences in descriptive characteristics between children with and without T1DM were tested by ANOVA. Seasonal differences in physical activity across all children were also analysed by ANOVA. We used mixed linear regression analyses to examine associations between children with vs without T1DM in total physical activity (cpm ⁄day), time spent in MVPA (min ⁄day)

and sedentary time (min/day), taking into account the repeated measurements of physical activity and sedentary time. Analyses were adjusted for gender, age and BMI SDS score. We also examined whether gender modified the association between diabetes status (with T1DM or healthy) and the outcomes of interest by modelling the interaction term (gender by diabetes status). The results from the mixed linear models are expressed as effect sizes (beta coefficients) and 95% confidence interval.

Paper II

Differences in mean values between groups were tested with ANOVA. Categorical variables were compared using the chi-square test.

Paper III

Data analyses were preceded by a power calculation that showed an 80% probability of detecting differences in intake of macronutrients between the two groups of children (those with and without T1DM), with 25 participants in each group.

The anthropometric data, energy intake, nutrients and food groups were presented as mean, standard deviation (SD) and range. Descriptive data for the children with T1DM and those in the control group were compared using the unpaired Student's t-test. The chi-square test was used to compare different groups with regard to the parents' education. Adjusted multiple linear regression analysis was used to assess whether the intake of energy, nutrients and food groups differed between the groups. The variables that were considered as confounders were age, gender, parental education, BMI SDS, and total energy intake.

Paper IV.

Differences in mean values between groups were tested with ANOVA. Categorical variables were compared using the chi-square test.

5 RESULTS

Children

Table 1 shows descriptive data for the participating children with T1DM and healthy control children; these are compared with data for all children in Sweden younger than seven years with diabetes and the non-participating children with T1DM from Gothenburg. Apart from a somewhat lower age (4.5 vs 5.4 years) and a higher frequency of pump treatment (71% vs 40%), there were no significant differences between the children participating in the study and children of the same age in SWEDIABKIDS.

Glycaemic control and plasma glucose monitoring

The participating children with T1DM had a mean HbA1c of 60 mmol/mol. Nine children with T1DM (38% of study participants) reached the treatment target of HbA1c ≤57 mmol/mol. Twenty children provided plasma glucose data from more than 150 days (median 320 days), see Table 2.

5.1 Paper I: physical activity

Sundberg F, Forsander G, Fasth A, Ekelund U. **Children younger than 7 years with type 1 diabetes are less physically active than healthy controls**. Acta Paediatrica 2012: 101; 1164-1169.

There were 24 children (12 girls and 12 boys) with T1DM and 26 healthy children (14 girls and 12 boys) in this part of the study.

Comparing children with and without T1DM

Children with T1DM were less physically active than healthy controls.

Overall, the difference in total physical activity between children with T1DM and healthy children was 11.2 cpm in autumn ($p = 0.035$) and 14.1 cpm in spring ($p = 0.10$), equivalent to approximately 15% lower total PA in children with T1DM compared to healthy controls, both in spring and autumn (Figure 2). The analyses for BMI SDS scores were further adjusted to explore whether the differences in physical activity were mediated by adiposity (Table 3), but the group effect estimates were materially unchanged for total physical activity (12.3 cpm/day, $p = 0.010$) and time spent in MVPA (16 min /day, $p = 0.006$).

Sedentary time was higher in children with T1DM than in healthy children: the children with T1DM spent almost 32 min more in sedentary activity ($p = 0.035$). Following additional adjustment for BMI SDS, sedentary time did not differ significantly between groups ($p = 0.21$).

Comparing girls and boys

Boys were more physically active than girls, measured as cpm. Boys spent more time in MVPA than girls.

For total physical activity, the magnitude of difference between boys and girls was equal to the difference between children with and without T1DM ($p = 0.001$). Similarly, for time spent in MVPA, the difference between boys and girls was equal to the difference between children with and without T1DM (16.0 min/day). In contrast, no significant difference between boys and girls was observed for sedentary time, suggesting that girls spent more time in light physical activity compared with boys (Table 3).

Diabetes and gender

No significant interactions between gender and diabetes status were observed for any of the physical activity variables or for sedentary time. While boys with T1DM were on average almost achieving the recommended level of 60 min daily of MVPA, girls with T1DM were clearly below this recommended level (Figure 2).

Age

Total physical activity and time spent in MVPA were higher, and sedentary time correspondingly lower, in older children compared with younger children. For example, for each additional year of age, time in MVPA was 7.5 min/day higher ($p < 0.001$). This suggests that the younger children spent a larger amount of time in light physical activity compared with slightly older children (Table 3).

5.2 Paper II: hypoglycaemia

Sundberg F, Forsander G. **Detection and treatment efficacy of hypoglycemic events in the everyday life of children younger than 7 yr.** Pediatric Diabetes 2014: 15: 34–40

There were 23 children (12 girls and 11 boys) with T1DM in this part of the study.

The overall frequency of hypoglycaemia was 2.1 events per child per day. All children had hypoglycaemic events in their CGM data. The following analysis is based on the hypoglycaemic events detected by CGM.

Only 9.2% of hypoglycaemic events overall, and 1.8% during the night, were symptomatic. Symptomatic hypoglycaemic events had a lower nadir glucose value than asymptomatic events, 3.0 mmol/l vs 3.2 mmol/l (p= 0.004).

In total, 128 (32%) of the CGM-documented hypoglycaemic events were also detected by SMBG. The detection rate was higher during the day than at night (39% vs 21%). The mean time from onset to detection of hypoglycaemia was 25 min in daytime and 101 min during the night. No hypoglycaemic event was reported in the logbook without being verified with a plasma glucose value.

Of the 404 hypoglycaemic events, 286 (71%) had a nadir glucose ≤3.6 mmol/l and 312 (77%) had a duration of 15 min or more.

Table 4 shows plasma glucose monitoring frequency and plasma glucose values during the two weeks with concurrent blinded CGM.

Severe hypoglycaemia

The number of severe hypoglycaemic events (adding events retrospectively for the entire diabetes duration and prospectively during the study year) was 10 in total (corresponding to 15 events per 100 patient years). Four children reported one event, one child reported two events, and one child reported four events of severe hypoglycaemia. All these six children provided fewer than 10 plasma glucose values per day in the two weeks of registration with CGM in parallel.

Reported treatment

Almost all detected hypoglycaemic events were treated with extra carbohydrates, either as a defined amount of carbohydrates or as a part of a

mixed meal. Information on treatment of hypoglycaemia was available in the logbook for 361 events.

No carbohydrates were given in 247 (68%) of the CGM-documented hypoglycaemic events; this includes undetected hypoglycaemias. Defined treatment with extra carbohydrates was given in 79 (22%) of the 361 events and a meal was given at the ordinary time in 35 (9.7%) of the events.

When treating hypoglycaemia with a defined dose of carbohydrates, the mean (SD) dose of rapidly resorbed carbohydrates was 0.3 (0.3) g/kg followed by 0.7 (0.7) g/kg of more slowly resorbed carbohydrates. Rapid-acting carbohydrates were given in the form of dextrose tablets, milk, juice, or soft drinks. The main source of more slowly resorbed carbohydrates was bread. A milk-based cereal drink was sometimes given as a combined preparation of rapidly and slowly resorbed carbohydrates.

Treatment efficacy

Untreated hypoglycaemic events resulted in early relapse (within three hours) into a new hypoglycaemic event, even if the first event resolved spontaneously in most cases (Table 5). Treating hypoglycaemias according to guidelines with a defined dose of carbohydrates resulted in glucose values well within target, whereas treatment with a planned mixed meal was followed by higher glucose values (see Paper II, Table 4).

5.3 Paper III: nutrition

Sundberg F, Augustsson M, Forsander G, Cederholm U, Axelsen M. **Children under the age of seven with diabetes are increasing their cardiovascular risk by their food choices.** Acta Paediatrica 2013 doi;10.1111/apa.12533

The participants in this part of the study were 24 children with T1DM (12 girls and 12 boys) and 27 healthy children (14 girls and 13 boys).

Comparison of food intake with recommended intake

Table 6 shows the food intake of the children with T1DM and the healthy children, compared with current recommendations.

The energy percent (E%) from total fat was within the recommendations of the International Society for Pediatric and Adolescent Diabetes (Smart 2009) and of the WHO/FAO for both groups (Uuay). Intake of saturated fat was above the recommended level of 10 E% (Smart 2009, Uuay), both for children with T1DM and for the healthy control group. In both children with

T1DM and the healthy children, the percentage of polyunsaturated fat was within the ISPAD recommendations but too low according to WHO/FAO recommendations. The ratio of polyunsaturated fat to saturated fat (PUFA/SFA) was the same in both groups.

The Swedish National Food Agency recommends that children of all ages should consume low-fat milk (containing less than 0.7 g fat per 100ml) daily. All children (with and without T1DM) in the DU7 study consumed cow's milk, and four of the children with T1DM and three of the healthy children were given low-fat milk at home.

Two of the children with T1DM and eight of the healthy children consumed spreads labelled as a healthy choice by the Swedish Food Agency (oil-based spreads containing less than 41% fat, of which no more than one third is saturated) at home.

The children with T1DM had lower E% from carbohydrates than recommended (Smart 2009) Intake of fruit, vegetables and juice was lower than the recommended 400 g per day (Mann) both in children with T1DM and in healthy children. The intake of dietary fibre was below the recommended level (Smart 2009) in both the T1DM group and the control group.

The E% from protein was higher than the recommended level (Smart 2009), but only in the children with T1DM.

Comparison between children with and without T1DM

The children with T1DM had a lower intake of carbohydrates, expressed both as E% and g/kg, and they had a higher E% from fat and protein. The intake of both monosaccharides and disaccharides was lower in children with T1DM than in healthy children.

There was no difference between the two groups in total energy intake (Table 6).

Total intake of fruit and vegetables, including juice, did not differ significantly between the groups but, concerning juice alone, children with T1DM had a lower intake.

Neither the intake of dairy products nor the intake of calcium differed between the groups (Table 6).

There was no significant difference in number of fish servings per week (3.0 ± 2.0 in children with T1DM and 2.1 ± 1.2 in healthy children).

Correlation between total fat intake and other dietary factors in children with T1DM

There was a negative correlation between the E% of fat and intake of fruit and vegetables in children with T1DM (Figure 4) but not in healthy children (r = -0.32). There was no correlation between diabetes duration and intake of fat or of fruit and vegetables.

The higher the total fat intake, the higher was the proportion of saturated fat (Figure 5). The main sources providing saturated fat were dairy products (26%), meat products (25%) and added fat (18%) such as spread.

5.4 Paper IV: health-related quality of life and glycaemic control

Sundberg F, Sand P, Forsander G. **Health-related quality of life and glycaemic control in pre-school children with diabetes.** (Submitted).

The participants in this part of the study were 24 children (12 girls and 12 boys) with T1DM and 27 healthy children (14 girls and 13 boys). Data were partly missing from one parent of a child in the older group (≥5 years) with T1DM, thus 23 parents (of 11 girls and 12 boys) with T1DM contributed proxy reports for their child regarding generic HRQOL.

HRQOL

There was a clear correlation between generic and diabetes-specific HRQOL, both when self-rated by the child ($r=0.85$, $p<0.01$, $N=10$) and when rated by the parent ($r=0.77$, $p<0.01$, $N=23$ due to missing data from one parent). Thus, convergent validity of the questionnaires was confirmed.

Children with T1DM had lower HRQOL than healthy children, as rated by their parents. (Table 7a and 7b). This was true for the entire group of children and remained significant in the younger age group when dividing data into two age-based subgroups (<5 years and ≥ 5years).

When comparing individual child–parent dyads, there was no correlation between the parent's rating and child's own rating of HRQOL (either generic or diabetes-specific). There was no systematic pattern of the child or parent scoring the child's HRQOL higher or lower. On a group level, there were no significant differences in total scale score when comparing HRQOL rated by children or by parents (Table 7).

Four out of ten of the older children (aged 5–6.9 years) with T1DM scored their own generic HRQOL below the suggested at-risk level of concern: 1 SD below a general population (Varni 2003). Five out of 23 parents (22%) scored their child's generic HRQOL below the same cut-off level of concern. A comparison between the children with at-risk HRQOL and the remaining children revealed no identifiable differences in insulin delivery mode (pump or injections), number of plasma glucose values per day, HbA1c, glucose variability, hyperglycaemia, hypoglycaemia or BMI SDS.

One of the 10 children in the age group 5–6.9 years scored his diabetes-related HRQOL as more than 1 SD below the rest of the study group. Two out of 24 parents (8%) in the entire T1DM study group scored their child's diabetes-related HRQOL at the same low level. Both these two children with low parent-rated diabetes-related HRQOL were pump-treated boys with diabetes duration of less than one year. They could not otherwise be discriminated from the study group with respect to treatment outcome (HbA1c, glycaemic variability, hypoglycaemia or hyperglycaemia) or treatment aspects (plasma glucose monitoring). No group statistics were analysed, due to the low number of children reporting an at-risk low level of diabetes-related HRQOL.

There was no difference in either generic or diabetes-related HRQOL (as scored by child or parents) related to parental education, immigrant status or cohabitation of parents.

HRQOL, insulin treatment and glycaemic control

There was no association between any treatment aspects, such as mode of insulin delivery (insulin pump vs injections) or number of plasma glucose values per day, and HRQOL. Neither was there any correlation between HRQOL and any treatment outcome (HbA1c, hyperglycaemia, hypoglycaemia, glycaemic variability or BMI SDS).

5.5 Review of the hypotheses

- The first hypothesis ("Preschool children with T1DM have good glycaemic control according to HbA1c results, but the proportion of time spent within the blood glucose target range is not satisfactory") is supported in Paper IV.
- The second hypothesis ("Both over- and under-treatment of real or suspected hypoglycaemias contributes to fluctuating plasma glucose levels") is supported in Paper II.
- The third hypothesis ("preschool children with T1DM are less physically active than healthy children of the same age and gender") is supported in Paper I.
- The fourth hypothesis ("fear of hypoglycaemia is associated with less physical activity") is not yet tested, as the data analysis is still ongoing.
- The fifth hypothesis ("on average, preschool children with T1DM have the same intake of energy and macronutrients as healthy children of the same age and gender") was supported (i.e. not overthrown) in Paper III.
- The sixth hypothesis ("increased day-to-day variability in energy intake is associated with poorer glycaemic control, measured as both HbA1c and time spent within the plasma glucose target range") was partly supported in an abstract presented at the ISPAD annual meeting 2010 (Sundberg).

6 DISCUSSION

The high glycaemic variability and high frequency of undetected hypoglycaemias shows that glycaemic control in young children with T1DM leaves room for improvement. The high number of undetected and thus untreated, hypoglycaemic events warrants improved methods of care, in particular the use of modern technology such as real-time CGM.

The high testing frequency during both day and night can be seen as an indicator of parental stress and of the limitations of SMBG as the only source of information regarding glycaemia in everyday insulin treatment of young children with T1DM.

The reported non-optimal eating habits and low physical activity – especially in combination – raise strong concerns regarding the future cardiovascular health of today's young children with T1DM.

The low HRQOL that emerged shows that the wellbeing of young children with T1DM needs more attention from diabetes teams.

Insulin substitution

Current methods of insulin treatment have several limitations. Insulin is given subcutaneously instead of centrally into the portal vein. The most obvious sign of non-physiological insulin substitution is dysglycaemia. The participants in our study showed, not surprisingly, all signs of dysglycaemia (hyperglycaemia, high glycaemic variability and frequent hypoglycaemia) despite an HbA1c value on average just slightly above the treatment target level.

Subcutaneously administered insulin has a delayed onset of action and a more prolonged action than centrally secreted insulin. Physiologically, insulin is instantly secreted on demand round the clock, mainly regulated by glucose levels. Thus, dysglycaemia can be the consequence of giving the wrong amount of insulin but also of a time mismatch between insulin need and its availability.

Glycaemic variability in the DU7 study, expressed as SD, was 4.4 mmol/l (Paper II). This is slightly below what has recently been reported by Danne et al. in MDI-treated preschool children with T1DM (Danne). It represents more than four times the glycaemic variability of healthy children aged 8–15 years

according to JDRF (JDRF 2010), and almost double the variability of children who have T1DM with some remaining excretion of C-peptide (Sherr). It is markedly above the suggested target of less than 3.5 mmol/l. The lack of consensus regarding methods of reporting glycaemic variability makes comparisons between studies difficult. The high glycaemic variability of young children regardless of mode of insulin treatment has been reported previously (Alemzadeh, Jeha, Patton 2012).

Intervention studies aiming at reducing glycaemic variability are scarce, especially in preschool children with T1DM. One interesting example is the ONSET study (Kordonouri 2010), in which children aged 1–16 years were randomly assigned to either ordinary pump treatment or sensor-augmented pump therapy from the onset of insulin treatment. The intervention lasted for one year and it was observed that those children who used the sensor-augmented pump therapy showed less decline of C-peptide secretion and less glycaemic variability (despite equal HbA1c) two years after diagnosis than those children who were randomised to ordinary pump treatment without CGM or for other reasons did not use the CGM (Kordonouri 2012).

Subcutaneous insulin delivery creates an imbalance between peripheral insulin and insulin available for the liver. Usually the liver is the target organ for approximately 50% of secreted insulin.

A well-established marker of a lack of liver insulinisation in subcutaneous insulin treatment is a low level of insulin-like growth factor 1 (IGF1). The absence of negative feedback increases levels of GH, which in turn induces peripheral insulin resistance. This is a major concern when treating adolescents with T1DM with insulin and adjunct therapy with IGF1 has been tried (Acerini).

Codner et al. (Codner) has shown that girls with T1DM have higher levels of adrenal androgens and anti-Müllerian hormone (as in polycystic ovarian syndrome) even at the age of six years. This has been interpreted as an effect of peripheral adrenal and ovarian over-insulinisation due to subcutaneous insulin treatment. Elevated markers of adrenal androgens in urine have been shown in both boys and girls younger than 10 years with T1DM (Remer). This might be regarded as one among many examples of the effects of peripheral over-insulinisation with secondary effects on endocrinology.

As with the national registry data from SWEDIABKIDS, our study participants (Paper IV) had a clearly elevated BMI SDS, which indicates that

overweight is a common marker of poor nutrition or metabolism in young children with T1DM.

It has been shown that near-normal glycaemic control can be reached overnight (i.e. when fasting) with closed-loop solutions, in which insulin delivery is computerised and delivered by a pump and glycaemia is monitored by subcutaneous CGM (Nimri, Elleri). In adolescents (mean age 13.6 years), glycaemic variability was reduced overnight to 1.6, and they were within glycaemic range 3.91–8.0 for 60% of the time (Kumareswan, Hovorka). Closed loop insulin administration has also been tested for a short time in laboratory inpatient settings in a small group (N=10) of children younger than seven years with T1DM (Dauber). When this solution becomes available in everyday treatment, it will probably improve glycaemic control in many patients with T1DM and thus reduce the risk of microvascular and macrovascular complications. The problems arising from the subcutaneous administration of insulin will prevail until other methods of insulin delivery are made available.

The tools currently available to mimic the complex physiology of insulin secretion are rather blunt and the methods of monitoring glycaemic control are not optimal. The task of managing the situation is, to say the least, demanding. The knowledge that erratic problem-solving puts the child's health and future survival at risk is distressing for the family and other caregivers. The challenge for the paediatric diabetes team is to support the child and family in achieving realistic hope and salutogenic competence.

The main source of the young child's present and future salutogenic capacity is the parent's approach to life and their way of tackling demanding situations (Antonovsky). Giving the parents a high sense of coherence regarding the treatment of the child's diabetes is thus of great importance. High glycaemic variability in the child with T1DM can be perceived as chaotic and thus reduce the parents' confidence that they can predict and control the outcome of a given situation, for example a meal, with a chosen insulin dose. More sophisticated technological equipment – such as modern real-time CGM – can provide better information to support decision-making.

Detection of hypoglycaemic events

Iatrogenic hypoglycaemia has been a problem ever since life-saving insulin treatment was introduced in the early 1920s. Fletcher and Campbell wrote guidelines (Fletcher) for treatment of iatrogenic hypoglycaemia that have been given to and followed by insulin-treated patients for decades. Fletcher and Campbell gave the sound advice that everyone on insulin treatment

should be well acquainted with their symptoms of hypoglycaemia and should always carry sugar with them to be able to counterbalance the hypoglycaemia. In our study, the main problem was that the vast majority (90% of all and 98% of night-time) hypoglycaemic events in young children are asymptomatic and thus depend upon monitoring to be detected. Only one third of all hypoglycaemic events were detected in a patient group with a SMBG testing frequency of on average 10 plasma glucose values per day (Paper II).

Does detection of an asymptomatic condition matter? Yes, definitely, if that condition puts the affected person at risk of harm. A major concern in adult diabetes care is the risk of driving accidents during hypoglycaemia. When experienced car drivers with insulin-treated diabetes took part in a hypoglycaemic clamp study in a driving simulator, they only detected (and intended to treat) about 50% of hypoglycaemic events. Driving was poorer during hypoglycaemia and, if the task had not been conducted in a simulator, the drivers would have been at obvious risk of causing a fatal accident (Cox 2010). Preschool children do not drive cars but they perform other activities demanding high psychomotor precision, for example, learning to skate, swim, climb trees and ride a bicycle. Such skills are essential to many aspects of a young child's social life and one can wonder whether this contributes to the low physical activity reported in Paper I and the low sport grades in compulsory school of children with early-onset diabetes, as reported by Persson et al. (Persson).

Recurrent mild hypoglycaemic events put the child at risk of more severe hypoglycaemic events leading to coma or seizures (Cryer, Cox 2007).

Repeated, untreated hypoglycaemic events feed the vicious circle of hypoglycaemia unawareness. In this age group, hypoglycaemia unawareness is probably combined with age-appropriate cognitive immaturity and difficulties in understanding bodily sensations such as those signalling hypoglycaemia. This makes hypoglycaemia even harder to detect, which can explain the higher frequency of undetected hypoglycaemic events in our study compared with studies focusing on subjective identification of hypoglycaemia symptoms by older children and adults (Gonder-Frederic 2008, Cox 2010). In a field study, parents of children aged 6–11 years failed to detect 54% of hypoglycaemic events and the children themselves failed to detect 41% of events (Gonder-Frederic 2008).

It is also well known that even mild hypoglycaemic events impair cognition and learning (Ryan 1990, Gonder-Frederic 2009, Clarke 2009). Early childhood is a period of intense learning, and the diabetes team should aim to

support the child with T1DM to achieve his or her potential under optimal conditions. The effects of diabetes on school grades are largest in children with early-onset diabetes and this effect is most apparent in the lower part of the grade scale (Persson). This suggests that the children who already find it hardest to cope in school pay the highest price for having diabetes from an early age.

Teaching initiatives to increase hypoglycaemia detection rate among insulin-treated adults have been tried with varying results (Cox 2001). The probability that this kind of programme would work in preschool children is very low. In our study, caregivers were encouraged to note anything that made them suspect an ongoing hypoglycaemic event when testing the child's plasma glucose; this box in the diary was almost always empty, indicating an absence of identifiable hypoglycaemia symptoms (Paper II). The basis of awareness training must be that there is some symptom that can be detected by the parent or caregiver.

Hyperglycaemia also has detrimental effects on immature brains (McCrimmon), in addition to other complications (Nathan), and yet it is common practice to allow blood glucose levels to reach the hyperglycemic range in this age group in order to avoid hypoglycaemia at all costs (ADA 2014, Wood). This is unsafe and treatment should instead aim to minimise both hyperglycaemia and hypoglycaemia in an effort to achieve normoglycaemia.

ISPAD recommends a plasma glucose testing frequency of 4–6 tests per day in insulin-treated children in order to achieve good glycaemic control (Rewers). Plasma glucose testing habits varied largely in the DU7 patient group (3–28 tests per day, Paper I and Paper IV), but the mean testing frequency was 9.7 tests per day; this is approximately double the rate recommended in the ISPAD guidelines. For most of the participating children it does not seem reasonable to increase the plasma glucose testing frequency further, since every test means that the child and the caregivers have to interrupt other activities to focus on the testing and perform a finger prick.

The data from the two weeks of diary notes with SMBG and data from the entire year from each child clearly showed fairly stable testing habits. Thus, it is reasonable to assume that the nocturnal testing frequency of 1.8 tests per night represents the typical pattern throughout the year.

The technique of real-time subcutaneous CGM has evolved during the last fifteen years. Despite technical and practical limitations, it has proved a

useful tool in toddlers and preschool children with T1DM (Tsalikian, Kordonouri 2010).

Treatment of hypoglycaemia

The use of blinded CGM in this study gave us the opportunity to investigate how hypoglycaemic events were resolved. According to the ISPAD guidelines, an ideal treatment of hypoglycaemia should elevate the glucose value to 5.6 mmol/L within 15–30 minutes (Clarke). Events detected by the caregivers could be treated with a defined dose of extra carbohydrates or by providing a planned mixed meal. To describe the different outcome of these two possible strategies we categorised treated events according to type of response. Our results can serve as an evaluation of the efficacy of the ISPAD guideline to give 0.3 g/kg of rapidly absorbed carbohydrates, which was confirmed as appropriate (Paper II). The result of serving a planned meal as a treatment of hypoglycaemia more often resulted in hyperglycaemia. From this, the practical advice can be derived to first treat the hypoglycaemic event with rapidly absorbed carbohydrates and then choose an insulin dose appropriate for the planned meal and following activity as if plasma glucose were within the target range.

The majority of hypoglycaemic events in our study went undetected and thus were not actively treated. Some of the episodes were very mild and of short duration, as indicated by the CGM data, but 71% had a nadir glucose of ≤3.6 mmol/l and 77% had a duration of 15 minutes or more (Paper II). The restoration of normoglycaemia could then possibly have been a combination of the declining effect of a previously given insulin dose and the hormonal counterregulation of hypoglycaemia. Untreated hypoglycaemic events were not generally followed by hyperglycaemia, indicating that hyperglycaemia after hypoglycaemia can be attributed to overtreatment rather than to overshooting in hormonal counterregulation. This finding also supports the advice to treat hypoglycaemia events with a defined dose of carbohydrates to avoid causing hyperglycaemia. This is crucial, as the combination of hypoglycaemia followed by hyperglycaemia might lead to extreme metabolic stress in the central nervous system (McCrimmon).

The observation that most hypoglycaemic events are resolved regardless of treatment was presented as early as the 1920s by Fletcher and Campbell. They also reported that untreated hypoglycaemic events tend to relapse,

which was confirmed in our data. Whereas only a minority (36%) of treated hypoglycaemias relapsed within three hours, the majority (55%) of untreated events did so, a difference that is both statistically significant and clinically relevant. Detection and appropriate response to a hypoglycaemic event seems to effectively reduce the risk of serial hypoglycaemic events, which are associated with increased risk of severe hypoglycaemia (Cox 2007).

Affecting lifestyle factors in preschool children

There is no contradiction between population-based interventions to promote increased physical activity or better food choices and interventions that are to be seen as a part of the diabetes care delivered by the diabetes team. Young children with T1DM would probably benefit from both efforts, but population-based interventions are not likely to be enough to meet the special needs of children with T1DM.

A meta-analysis of the effectiveness of public health interventions to promote increased physical activity in preschool children showed that these interventions have a small to moderate effect on general physical activity and a moderate effect on MVPA. Most effective were interventions in day care centres involving outdoor activities and unstructured activity. Home-based interventions and educational initiatives aimed at increasing physical activity were less effective (Gordon). It has been shown that outdoor playing and spacious outdoor playing environment is associated with increased physical activity (Boldemann). In a Danish observational study it was concluded that locating the day care centre within the playground and providing more indoor space per child were design factors associated with higher levels of objectively measured physical activity (Groenholt Olesen). This finding can at least partly explain the observation in our study (Paper I) and others (Hesketh 2014) that children are less physically active during autumn and winter; physically active play demands space.

Observational data show a correlation between objectively measured parental physical activity and the physical activity of the preschool child (Hesketh). It is also observed that parents who watch TV more than two hours per day have preschool children who have a fivefold increased risk of following suit (Jago).

Similarly, children follow the eating habits of their parents and entire family (Fisk, Christian, Raynor), and this has been found to influence children's food habits throughout their lives (Kaikkonnen). For practical reasons, very

young children are dependent on what food is served in their environment. What is served at home is a consequence of more-or-less active choices made by the parents. For institutions such as day care centres, there are practical recommendations from the Swedish Food Agency for implementing the Nordic Nutritional Recommendations.

No nutritional intervention studies aimed at reducing cardiovascular risk by lifestyle modifications in children with T1DM were found in a review study published in 2009 (Rovner), and a PubMed search in January 2014 has identified no further studies. Our observational study contributes valuable input when planning such interventional studies to fill this gap.

The question can be raised whether it is ethical or not to urge the family to make lifestyle changes when they have just received the information that their child has got a lifelong disease with burdensome self-care and treatment; nonetheless, the question can also be turned around: is it ethical not to suggest changes to protect the child from future risks?

The interest of the child is to stay healthy, to learn good long-term strategies for managing her own life but also not to be subjected to unwarranted restrictions. The interest of the parents is to feel confident that they provide the best possible life, both qualitatively and quantitatively for their child (and any siblings). The main emotional stressor for parents is their concern for the child's future health (Haugstvedt), expressed as fear of diabetes complications (Haugstvedt). If the child has siblings, their interest is to have parents who feel emotionally strong enough to be capable of taking care of all their children; the siblings usually care about their sister or brother with T1DM and wish the child the best possible future health. All family members statistically benefit from a reduced risk of cardiovascular disease after changing their lifestyle. Their only loss is usually the initial burden of changing their habits and a perceived curtailing of enjoyable habits, such as restrictions on certain foods and less time available for watching TV or sitting at the computer.

There are clear benefits to society if children with T1DM grow up to be healthy citizens with fewer costly diabetes complications, paying more tax by working more over a longer period than has been possible in the past. The only burden to society might be the need to invest in individualised health care, supporting the family to make the necessary lifestyle changes.

Thus, it probably is unethical not to support families with a young child with T1DM to make lifestyle changes. Today's research suggests that the most

efficient strategy is when the parents change their own lifestyle and include their children in the new household habits (Hesketh 2012, Jago, Fisk, Christian).

Nutrition

Our finding that children younger than seven years with T1DM eat too much saturated fat and too little fruit, vegetables and fibre is in line with findings in older children with T1DM, reporting that few of them meet nutritional recommendations (Patton 2011). Two studies (Virtanen and Maffeis) show, in contrast to the others, that families of children with T1DM are willing and capable of meeting the child's need for a diet that will reduce the risk of cardiovascular disease. The Virtanen study is a two-year follow up of children younger than six years with T1DM. They found that intake of vegetables declined and intake of fat increased somewhat during the period but that children with T1DM met the recommendations regarding food intake and ate more vegetables than healthy children. In the Maffeis study on children and adolescents aged 6–18 with T1DM, they were found to meet nutritional recommendations and they had healthier eating habits than healthy children and adolescents from the same geographical area. Virtanen gives no clear description of how the families were educated on the nutritional component of T1DM treatment; Maffeis reported that the families met a paediatric diabetologist four times and a dietician twice per year in the diabetes polyclinic as a part of routine care. Virtanen used a combined method of a recall interview on two days and prospective food records for three days, whereas Maffeis used interview by a dietician as the data collection method.

In our study, we did observe that some children with T1DM had a combination of a high intake of fat and low intake of fruit and vegetables. The diabetes team should identify those children whose pattern of food intake is associated with a very high risk of cardiovascular disease and give extra support to their families to change their dietary habits. Maffeis reported that a part of their clinical routine was that the patient or family met with a dietician twice yearly. ISPAD guidelines recommend that a dietician should review the nutrition of a child with T1DM at least annually (Pihoker).

Our study also found that the mean daily intake of fruit and vegetables in children with T1DM was approximately half of the recommended level. A recent British study shows that the most important factors associated with a higher intake of fruit and vegetables in young children are that the family eats meals together at a table, that the parents eat fruit and vegetables themselves and that the parents facilitate the child's eating by serving cut pieces of fruit

and vegetables (Christian). Serving fruit between meals may present a special challenge in children with T1DM, as it might lead to elevated blood sugar. In very young children with small total insulin doses per day, the normal carbohydrate content of a fruit serving (10–20 g) is not usually matched by the basal insulin dose. One practical piece of advice could therefore be to emphasize the importance of serving fruit at the end of every meal and snack, when there is sufficient insulin coverage.

The high intake of saturated fat is worrisome because of the high risk of cardiovascular disease in children with T1DM. The main sources of saturated fat were dairy products, meat products, and added fat, such as spreads (Paper III) and these groups of food could be targeted in counselling the families about what kind of food to buy and have at home.

Physical activity

Our finding that preschool children with T1DM are less physically active than healthy children is in line with findings on older children with T1DM (Särnblad, Heilman).

It is essential to use objective methods when studying physical activity and other socially desirable lifestyle factors. Heilman presented a clear example of the unreliability of subjective reports of physical activity compared to objective data (Heilman). Fortunately, accelerometer-based studies in recent years have contributed more detailed knowledge regarding the physical activity of young children.

Outdoor play is associated with increased physical activity (Boldeman). Studies comparing weekend days to weekdays show a different distribution of physical activity and, in one study, lower levels of physical activity during the weekend (Brasholt). Another study shows equal physical activity on weekdays and weekend days (Hesketh 2014). Data from weekdays vs weekend days were not compared in our study. When designing physical activity interventions to reduce the risk of cardiovascular disease in children it is important to focus on high-intensity physical activity to be most effective (Ekelund). Emphasising the importance of playing outdoors at weekends could be a topic in family-based interventions to promote increased physical activity in children with T1DM.

Our finding that girls spend more time in light physical activity is consistent with other studies, both in preschool children in western countries (Brasholt, Hesketh 2014, Boldemann) and in older children and adolescents (10-17 years) in rural Kenya (Ojiambo). Regardless of the cause of lower physical

activity in young girls than in young boys, young girls with T1DM will eventually become adolescents and women with high cardiovascular risk (Laing) and thus in need of extra encouragement to increase their physical activity levels. Establishing these habits at an early age would be especially beneficial.

Physical activity has several positive effects on cardiovascular risk and metabolic health. Being physically active is also necessary in order to acquire and improve gross motor skills (O´Neill). Lower physical activity from an early age in children with T1DM can thus be a contributory factor behind their lower sports grades in compulsory school compared to healthy peers (Persson).

Children with T1DM generally demonstrate lower average cardiovascular fitness than healthy children of the same age (Lukacs, Williams). When comparing prepubertal boys (Heyman) and adolescent boys and girls (Adolfsson) with T1DM to healthy controls matched for physical activity, age and gender, there was no difference in fitness between the children with and without T1DM. This implies that the lower fitness in children with T1DM (Lukacs, Williams) could be a consequence of their lower levels of physical activity (Särnblad, Heilman) and thus could be improved by increased physical activity. Our study contributes the information that the lower levels of physical activity in children with T1DM are already present before the children themselves can make active decisions regarding participation in physical activity.

Identifying and eliminating factors that restrict physical activity in children with T1DM could contribute to closing this gap. In adults on insulin treatment, fear of hypoglycaemia is sometimes an obstacle to physical activity (Brazeau). Whether parental fear of hypoglycaemia contributes to their child's lower physical activity is not known; we have collected data to explore this but these data have not yet been analysed. Other contributing factors in the lower levels of physical activity in children with T1DM could be interruptions of play due to treatment procedures such as SMBG testing. It would be worth exploring whether new techniques – especially remote real-time CGM monitoring, which allows the caregiver to monitor the child's current glucose levels without interrupting the flow and intrinsic logic of playing – could contribute to increased physical activity in preschool children with T1DM.

Some countries (Canada, Australia, the UK and USA) have changed their recommendations on physical activity in preschool children from 60 minutes

of MVPA to 180 minutes of any intensity of physical activity per day. Hesketh et al has questioned the usefulness of this recommendation (Hesketh 2014) because it is already met by all children and the reduction in the risk of cardiovascular and metabolic problems might be too low (Steele, Ekelund). The Swedish recommendation is at least 60 minutes per day of MVPA for all children.

The child's HRQOL today, tomorrow and beyond

The low HRQOL identified in our study, especially in the children younger than five years, needs attention from the diabetes team and researchers. Screening according to ISPAD guidelines should not exclude the youngest patients, especially not as screening tools are available from the age of two years.

In our study we could not identify any treatment-related aspect associated with higher or lower HRQOL. This finding is in line with a larger Norwegian study that not did identify any difference in HRQOL in children treated with an insulin pump or MDI (Frøisland). We did not see the association between lower HbA1c and higher HRQOL that has been described in older children (Hoey, Frøisland). The absence of an association could indicate that the burden of T1DM and treatment is so heavy in itself that it outweighs the smaller differences from treatment mode or efficacy of glycaemic control. It could also be a consequence of the limited size of our study.

A German study of 840 young people aged 11–21 years with early-onset diabetes (diagnosed before the age of five years) showed that high HRQOL was associated with low HbA1c and high treatment satisfaction. Girls reported lower HRQOL than boys. Reported hypoglycaemia was associated with lower HRQOL (Stahl). In Italian men and women aged 30 years, HRQOL was better in those who developed T1DM before the age of five years than in those who were older at diagnosis (Trento). This phenomenon has also been described in adolescents with T1DM in low-income India (Puri).

In a Finnish study published in 2013, HRQOL in people with a mean age of 29 years and a mean diabetes duration of 23 years, HRQOL was equal to an age- and gender-matched control group in the general population, as long as no significant retinopathy was present. In the subgroup of patients with proliferative retinopathy, HRQOL was significantly lower, both compared with other people with T1DM and with the general population (Hannula). The participants in the DCCT/EDIC study were adolescents or adults at diagnosis. Their HRQOL have been followed as an integrated part of the

study and three conclusions have been drawn: first, there was no difference in HRQOL between the intervention group and the control group; second, lower HbA1c was associated with higher HRQOL and third, the development of complications was clearly associated with a deterioration in HRQOL and more complications, or more severe ones, were associated with a larger deterioration in HRQOL (Jacobsson).

The aim of insulin treatment in T1DM is to retain health and quality of life in the short and long term. Supporting good glycaemic control in combination with psychosocial support from diabetes onset is essential to achieve this in a lifelong perspective.

Supporting the parents

The parents are the child's main source of the salutogenic capacity needed to handle the lifelong challenge of insulin treatment (Antonovsky). The parents are also responsible for the practical implementation of insulin treatment in the everyday life of the preschool child with T1DM; they make almost all the decisions related to insulin treatment and the child is totally dependent on their practical choices. Everything a very young child eats is provided by someone else, mainly the parents and the staff at the day care centre. The child can influence the situation only by eating or refusing to eat; the preschool child cannot, as the teenager can, decide to buy something else to eat instead of the suggested food. The parents decide how much time the child should spend indoors or outdoors and supervises play activities. Furthermore, they regulate where to eat meals (at a table or in front of the TV or computer) and whether meals are eaten together at set times or individually on demand. Thus, the capacity of the parents to make good decisions is crucial for the child with T1DM.

The intense pressure on parents of children with T1DM is demonstrated in the high rate of parents with burnout symptoms in these families. A Swedish study by Lindström found that parents who feel a strong need to be in control are at extra high risk of getting burnout symptoms (Lindström). A Norwegian study by Haugstvedt showed that the largest emotional burden in both mothers and fathers was concern about the child's future health (Haugstvedt). In these studies, mothers expressed more symptoms of burnout (Lindström) and emotional distress (Haugstvedt) than fathers. Lindström found an association between signs of parental burnout and the extent to which the parents reported that their everyday life was affected by problems related to their child's disease (Lindström).

Both Haugstvedt and Lindström reported that an important factor affecting perceived parental burden and parental burnout was night-time care, such as SMBG, and night-time hypoglycaemic events (Haugstvedt, Lindström). In our study, families measured on average 1.8 plasma glucose values per night (range 0–5.7). Despite this, only 21% of night-time hypoglycaemic events were detected, and a contributing factor could be that 98% of the events were asymptomatic.

Lindström identified three factors protecting against parental burnout: first, shared responsibility between the parents for the child's treatment; second, having people in their network who are capable of taking care of the child and willing to do so sometimes; and third, having access to leisure time of their own and together (Lindström).

The role of the diabetes team is to help the parents to cope with the child's treatment needs. The family network needs support and education to enable friends and relatives to take care of the child for shorter periods, giving the parents access to some leisure time. From the perspective of the child, it is good to be able to trust that other significant adults, (for example, grandparents) are capable of helping them in their everyday life including basic diabetes treatment-related procedures.

New technologies, including real-time CGM with remote monitoring and, hopefully soon, closed-loop solutions, are likely to reduce the burden of parenting children with T1DM. Early adaptations of these technologies to the practical needs of preschool children are warranted. Since this patient group only constitutes 10% of the total population of children and adolescents with T1DM there is clearly a risk that the special needs of very young children will be overlooked if these technical developments are left to the judgement of commercial companies.

7 CONCLUSION

Treating T1DM in preschool children is a challenge for both the family and the diabetes team. The high glycaemic variability and high number of undetected hypoglycaemic events illustrate the need for new solutions. Modern knowledge about the complications of dysglycaemia makes striving for normoglycaemia imperative from diabetes onset. Real-time CGM should be made available to this age group from the onset of insulin treatment.

Early childhood is a window of opportunity for lifestyle interventions that last throughout life. If this is to be feasible, the entire family needs support from the diabetes team. The parents have to change their own habits in order to support their child. Improving eating habits and increasing physical activity is necessary to reduce the high risk of cardiovascular disease that is associated with diabetes.

The low reported HRQOL in the youngest children with T1DM needs attention from the diabetes team. These children should not be excluded from the HRQOL screening recommended for all children with T1DM. It is important for the diabetes team to use screening questionnaires validated in all paediatric age groups.

8 FUTURE PERSPECTIVES

The ultimate goal of diabetology is to prevent or cure diabetes. Until then, stepwise improvement of insulin substitution and strategies to reduce the risk of complications is the roadmap to sustained quality of life in individuals with T1DM.

Preschool children with T1DM often require different treatment strategies than older children, adolescents and adults with T1DM. The needs of very young children with T1DM have to be identified when developing new strategies and technologies for insulin treatment. Their cognitive, motor and social immaturity, as well as their small body size, have to be taken into consideration when designing new equipment, including sensors, pumps and (semi) closed-loop solutions for insulin delivery

It is important to include children younger than seven years in both epidemiological and clinical studies regarding treatment strategies and outcomes; moreover, when the youngest children with T1DM are included in these studies, data regarding children with early-onset diabetes must be presented separately to enable subgroup analysis.

Children younger than seven years with T1DM constitute approximately 10% of the population of all children and adolescents with T1DM. Cooperation between centres is necessary in order to give the studies enough power to detect differences and associations in the analysis.

Our study was observational by design and provides input into future interventions. In order to reduce the risk of cardiovascular disease, diabetes teams need to develop strategies to change food choices by the families of young children with T1DM; they should also design interventions aimed at increasing physical activity, especially in very young girls with T1DM. Further research on improving support to the parents of young children with T1DM is needed. Parents' capacity to understand, manage and bear the burden of their child’s treatment is crucial for the healthy survival of the child. Their capacity to pass this knowledge on to the child is necessary for the future. The diabetes team needs elaborated strategies to support this process.

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APPENDIX

Table 1. Description of participating children with T1DM ("DU 7 children") and the healthy control group. Data are also presented on all children younger than seven years with diabetes in Sweden from the Swedish paediatric diabetes quality registry, SWEDIABKIDS, and patients with diabetes from the Queen Silvia Children's Hospital who declined the invitation to participate in the study. Values are given as mean ±SD (range).

	DU 7 children (N=24)	Healthy Children (N=27)	SWEDIABKIDS (N=615)	Non-participants (N=29)
Age (years)	4.5±1.7 [1] (1.8–6.9)	4.6±1.6 (1.1–7.4)	5.4±1.4 [1] (0.75–6.995)	5.3±1.4 (1.3-6.9)
Gender (% girls)	50	56	44	45
Diabetes duration (years)	2.0±1.6 (0.6–5.4)	-	2.3±1.4 (0.25–6.3)	1.9±1.5 (0.3-5.1)
HbA1c IFCC (mmol/mol)	60±7.1 (48–73)	-	57±9.6 (29–98)	59±9.7 (44-90)
HbA1c NGSP (%)	7.6±1.7 (6.5–8.8)	-	7.4±3.0 (4.8–11.1)	7.5±0.89 (6.2-10.4)
Weight (kg)	20±5.0 [2] (12–31)	18.1±3.8 [2] (10.2–24.7)	22±4.9 (5.2–52)	21±4.8 (12-31)
Height (cm)	109±15 (87–137)	107±13 (77–126)	114±11 (65–145)	113±13 (83-131)
BMI (SDS)	0.63±0.81 [2] (-0.62–2.2)	-0.2±0.8 [2] (-2.5–1.0)	0.56±1.1 (-4.9–5.5)	0.45±1.1 (-1.7-2.4)
Insulin dose (U/kg/day)	0.69±0.23 (0.25–1.2)	-	0.76±0.26 (0.081–1.8)	-

% of insulin dose as basal dose	47±12 (21–67)	-	-	-
Insulin delivery mode (% pump)	71[1] [3]	-	40[1]	52[3]
Living with 2 cohabiting biological parents (%)	92	78		-
≥ 1 parent with > 12 years of education (%)	71	81		-

[1] The difference between the participants in the Diabetes Under Seven study and the Swedish Childhood Diabetes Registry SWEDIABKIDS is significant at the $p<0.05$ level.

[2] The difference between the participants in the Diabetes Under Seven study and the control group of healthy children is significant at the $p<0.05$ level.

[3] The difference between the participants in the Diabetes Under Seven study and the patients who declined the invitation to participate in the study is significant at the $p<0.05$ level.

Table 2. Plasma glucose data for the twenty children who provided data from 150 days or more.

N=20	Mean±SD (range)	Median
Number of days with data	315±60 (155–365)	320
Number of plasma glucose values per day	9.3±5.0 (3.2–27)	8.5
Mean plasma glucose (mmol/l)	9.3±1.2 (6.5–11.6)	9.1
Glucose variability (SD)	4.6±1.1 (2.5–6.8)	4.4
Percentage of values >10 mmol/l	37±10 (10–50)	37
Percentage of values ≤3.9 mmol/l	10±3.8 (5–17)	10

Table 3. Results from the mixed linear models, examining the association between (1) time spent in moderate and vigorous physical activity (MVPA) and diabetes status, gender, age and BMI SDS, and between (2) time spent sedentary and diabetes status, gender, age and BMI SDS (n=50).For more data, see Paper I, Table 2

	ß Effect size	95% confidence interval	p-value
MVPA (min/day)			
Male gender	16.0	6.1, 25.9	0.002
Age (per year)	7.5	4.5, 10.5	<0.001
Having diabetes	-16.0	-27.3, -4.6	0.006
BMI SDS	2.6	-3.6, 8.8	0.40
Sedentary time (min/day)			
Male gender	-10.5	-39.8, 18.0	0.48
Age (per year)	-11.7	-20.7, -2.7	0.011
Having diabetes	21.2	-12.3, 54.8	0.21
BMI SDS	13.2	-5.2, 3.16	0.16

Table 4. Plasma glucose testing (SMBG) of the participating children (N=23) during the two study weeks, one in autumn and one in spring.

	Mean ±SD	Range
Frequency of plasma glucose testing (values/24 h)	9.7 ±5.1	3.2–28
Frequency of plasma glucose measurement (values/night)	1.8 ±1.3	0–5.7
Mean plasma glucose (mmol/l)	9.1±1.4	6.5–13.5
Plasma glucose variability (SD)	4.4±0.90	2.4–6.5

Table 5. Hypoglycaemic events treated or not treated with extra carbohydrates. The difference between treated and untreated events was significant (p<0.001, chi-square test).

		New hypoglycaemic event within 3h	
		Yes	No
Treated (with added carbohydrates)	Yes	40	72
	No	136	111

Table 6. Food and nutrient intake in children under seven years with and without T1DM compared to current recommendations from ISPAD and WHO/FAO. Values are given as mean±SD (range).For further details see Paper III, Table 2.

	Children with T1DM (N=24)	Healthy children (N=27)	p-value	ISPAD	WHO/FAO
Energy MJ/kg	0.25±0.06 (0.13–0.35)	0.29±0.04 (0.22–0.36)	NS		
Total fat (E%)	35±5 (27–46)	31±4 (20–37)	0.001	30–35	30–40
Saturated fat (E%)	15±3 (10–22)	13±2 (8–17)	NS	<10	<10
Protein (E%)	18±3 (13–25)	15±2 (12–20)	0.015	10–15	
Protein (g/kg)	2.5 ±0.6 (1.5–3.4)	2.5± 0.4 (1.9–3.5)	NS		
Carbohydrates (E%)	47±6 (34–56)	54±4 (46–62)	<0.001	50–55	50–75
Dietary fibre (g/MJ)	2.3±0.7 (0.2–3.5)	2.4±0.5 (1.7–3.7)	NS	2.8–3.4	
Monosaccharides (g/day)	17±8 (5–39)	23±6 (14–37)	0.029		
Disaccharides (g/day)	39±17 (19–93)	54±16 (19–84)	0.034		

Fruit (g/day)	115±73 (0–236)	114±66 (0–251)	NS		
Vegetables (g/day)	62± 36 (10–158)	46± 31 (1–121)	NS		
Fruit, vegetables and juice (g/day)	191±98 (30–409)	207±75 (88–402)	NS	Regularly	400

Table 7. 7a.Health-related quality of life Total Scale Score reported by children with diabetes and their parents. Values are given as mean±SD (range).

	Children <5 yrs with T1DM* (N=14)	**Children ≥5 yrs with T1DM** (N=10)**	**All children with T1DM (N=24)**
PedsQL4.0 Generic Core Scales, child		76±18 (46–100)	
PedsQL4.0 Generic Core Scales, parent	79±13[1] (49–94)	81±16 (58–96) (N=9)	80±14[1] (49–96) (N=23)
PedsQL3.0 Diabetes Module Scales, child		75±15 (46–93)	
PedsQL 3.0 Diabetes Module Scales, parent	74 ±17 (28–94)	78±10 (65–95)	76±14 (28–95)

[1] The differences between children with T1DM and healthy children on the generic core scales rated by parents are significant at $p<0.01$.
* Proxy report by parent was used for children aged under five years.
** Self- and proxy report were used for children aged five years or above.

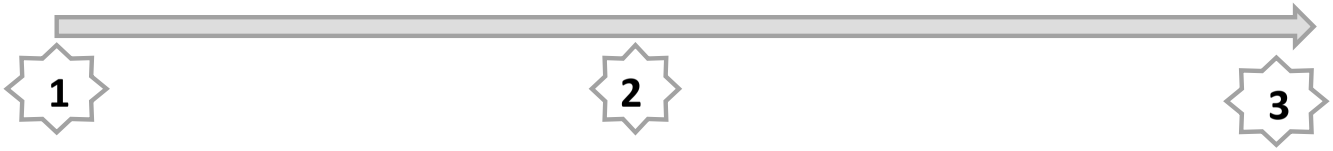
7b. HRQOL Total Scale Score reported by healthy control children and their parents.

	Healthy children <5 years* (N=16)	Healthy children ≥5 years** (N=11)	All healthy children (N=27)
PedsQL 4.0 Generic Core Scales, child		76.7±16 (46-98)	
PedsQL 4.0 Generic Core Scales, parent	93±4.4[1] (85–100)	89±7.5 (75–100)	91±6.1[1] (75–100)

[1] The differences between children with T1DM and healthy children on the generic core scales rated by parents are significant at $p<0.01$.
* Proxy report by parent was used for children aged under five years.
** Self- and proxy report were used for children aged five years or above.

Figure 1, study design

Study design



Week 1 + Week 2	
Children with T1DM	
Food diary (4 days) Accelerometer (all week) CGM (all week) Notes on treatment, symptoms of hypoglycaemia and plasma glucose values (all week)	
Healthy children	
Food diary (4 days) Accelerometer (all week)	

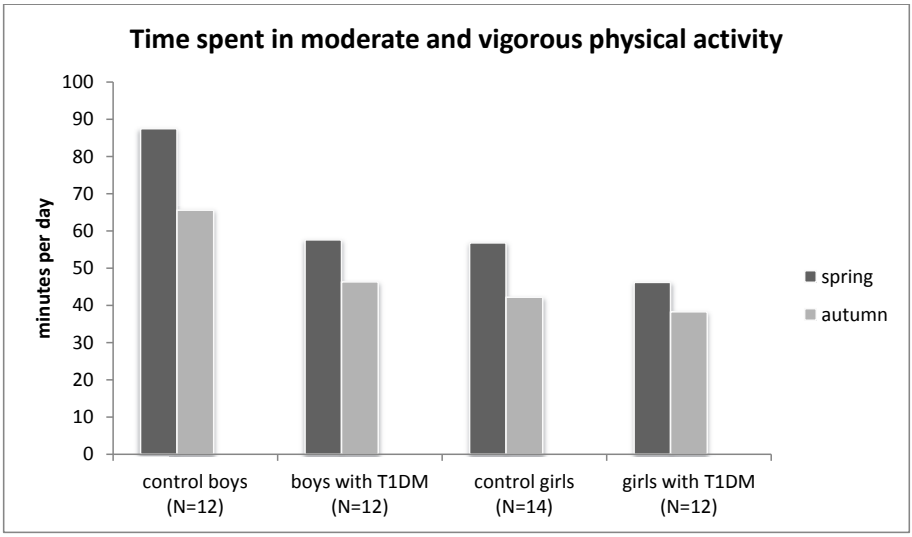


Figure 2 Physical activity in children with T1DM and healthy children during spring and autumn (n=50). Data are given as means. Overall, the difference in time spent in moderate and vigorous activity differed by 11 min/day (p=0.027) between children with T1DM and healthy children, after adjustment for season, age and gender. For more data see Paper I, Figure 1.

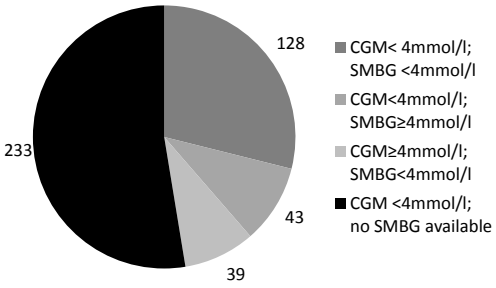


Figure 3. Hypoglycaemic events detected by CGM and SMBG. In total, 443 hypoglycemic events were registered, 128 (29%) of which were detected in both continuous glucose monitoring (CGM) and plasma glucose (SMBG). Of 82 events (18%) discordantly detected, 43 were only in CGM and 39 only in SMBG. In 233 events (53%), CGM was the only available data source. Of the 404 (443-39) CGM-detected hypoglycemic events,128 (32%) were also detected with SMBG. CGM = continuous glucose monitoring, SMBG = self-monitoring of blood glucose.

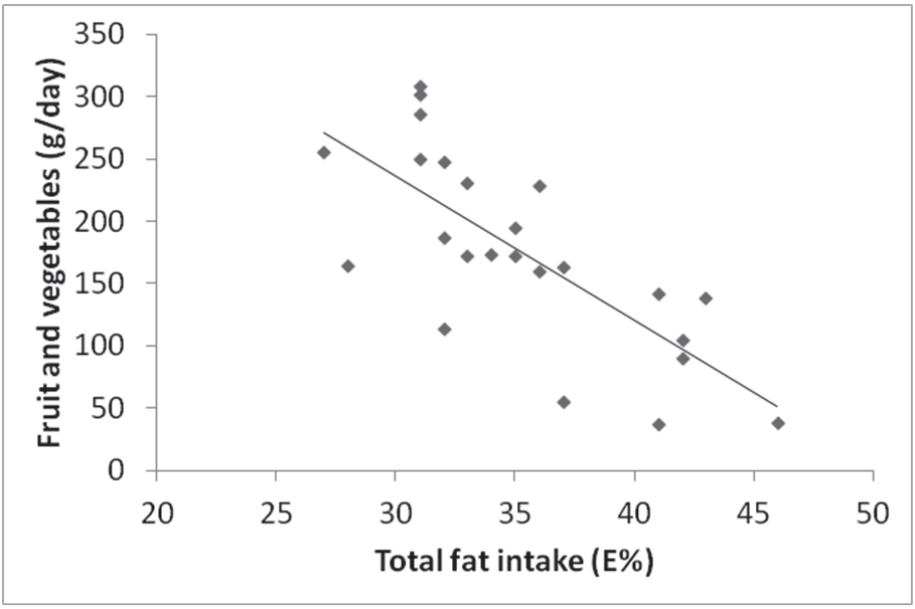


Figure 4. Correlation between intake of fat and intake of fruit and vegetables in children with type 1 diabetes mellitus ($r=-0.74$, $p<0.05$).

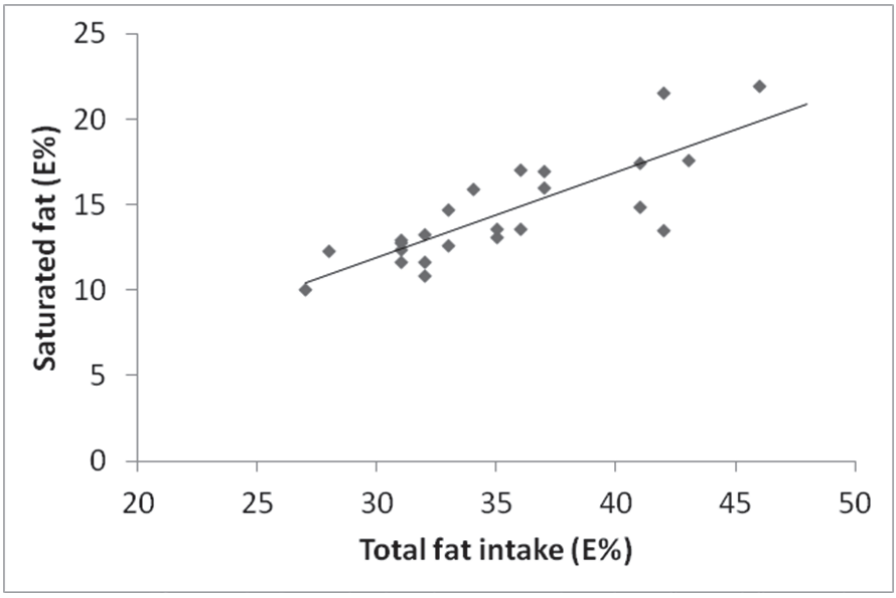


Figure 5. Correlation between intake of total fat and saturated fat in children with type 1 diabetes mellitus (r=0.82, p=0.05).