Clinical and biochemical characteristics of diabetes mellitus among children and young adults at onset and at development of complications

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on October 18, 2024, at 1.00 pm in the Segerfalk Lecture Hall, BMC A10, Sölvegatan 17, Lund

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Abstract:

Background: The prevalence of childhood type 1 and type 2 diabetes is increasing in Sweden and globally, leading to increased demands of better and more individualized management and treatment to reduce the risk of complications. This work studied children and adolescents, in a district in southern Sweden, diagnosed with type 1 diabetes between 1974 and 2021, and young adults with either type 1 or type 2 diabetes, participating in the national complications trial of the Diabetes Incidence Study in Sweden, K-DISS.

Results: No differences in glycemic control were found between insulin pump and pen treatment in a real-world pediatric type 1 diabetes setting with freedom of choice between these two modes of insulin delivery and with universal use of continuous glucose monitoring (CGM). CGM might be a stronger differentiator for glycemic control than the mode of insulin delivery.
Soluble endothelial selectin (sE-selectin) might be considered a potential predictor for development of diabetic retinopathy in type 2 diabetes. For soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1), no such predictive roles could be identified for type 1 or type 2 diabetes. HbA1c and clinical characteristics predicted development of diabetic retinopathy in type 1 diabetes.
Higher HbA1c was associated with shortened time to development of diabetic retinopathy, and a significant negative correlation was identified between the age at diagnosis of type 1 diabetes and the time to development of diabetic retinopathy.
In the studied district, the incidence of childhood type 1 diabetes has increased, despite immigration from areas with lower risk of diabetes.

Conclusions: This study confirmed the importance of keeping glycemic control as close to normal as possible to reduce the risk of complications. The search for new biomarkers for prediction of diabetic retinopathy should ideally continue with larger sample sizes, broader age ranges, and longer follow-up. CGM stands out as an important differentiator for glycemic control irrespective of pump or pen treatment. Importantly, quality of life and added benefits of automated insulin delivery systems are yet to be evaluated.

Key words: Type 1 diabetes, type 2 diabetes, childhood, HbA1c, glycemic outcomes, continuous glucose monitoring, insulin pump treatment, insulin pen treatment, diabetic retinopathy, soluble E-selectin, soluble ICAM-1, soluble VCAM-1, prediction, incidence, ethnicity, migration

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To Sophie, Caroline, and Magnus

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II. Ekelund C, Dereke J, Nilsson C, Landin-Olsson M

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PLoS ONE 2024; 19(6): e0304173.
https://doi.org/10.1371/journal.pone.0304173

III. Andreasson R, Ekelund C, Landin-Olsson M, Nilsson C

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Journal of Pediatric Endocrinology and Metabolism 2018; 31(4): 369-374.
https://doi.org/10.1515/jpem-2017-0417

IV. Ekelund C, Landin-Olsson M, Nilsson C

Increased incidence of childhood type 1 diabetes despite unaltered clinical characteristics at onset

Manuscript

Abstract

Background: The prevalence of childhood type 1 and type 2 diabetes is increasing in Sweden and globally, leading to increased demands of better and more individualized management and treatment to reduce the risk of complications. This work studied children and adolescents, in a district in southern Sweden, diagnosed with type 1 diabetes between 1974 and 2021, and young adults with either type 1 or type 2 diabetes, participating in the national complications trial of the Diabetes Incidence Study in Sweden, K-DISS.

Results:

I. No differences in glycemic control were found between insulin pump and pen treatment in a real-world pediatric type 1 diabetes setting with freedom of choice between these two modes of insulin delivery and with universal use of continuous glucose monitoring (CGM). CGM might be a stronger differentiator for glycemic control than the mode of insulin delivery.

II. Soluble endothelial selectin (sE-selectin) might be considered a potential predictor for development of diabetic retinopathy in type 2 diabetes. For soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1), no such predictive roles could be identified for type 1 or type 2 diabetes. HbA1c and clinical characteristics predicted development of diabetic retinopathy in type 1 diabetes.

III. Higher HbA1c was associated with shortened time to development of diabetic retinopathy, and a significant negative correlation was identified between the age at diagnosis of type 1 diabetes and the time to development of diabetic retinopathy.

IV. In the studied district, the incidence of childhood type 1 diabetes has increased, despite immigration from areas with lower risk of diabetes.

Conclusions: This study confirmed the importance of keeping glycemic control as close to normal as possible to reduce the risk of complications. The search for new biomarkers for prediction of diabetic retinopathy should ideally continue with larger sample sizes, broader age ranges, and longer follow-up. CGM stands out as an important differentiator for glycemic control irrespective of pump or pen treatment. Importantly, quality of life and added benefits of automated insulin delivery systems are yet to be evaluated.

Populärvetenskaplig sammanfattning

Bakgrund: Förekomsten av såväl typ 1 som typ 2 diabetes ökar bland barn både i Sverige och i världen som helhet. Detta leder till ett ökat behov av bättre och mer individualiserat omhändertagande och behandling av patienterna för att minska risken för komplikationer till diabetessjukdomen på lång sikt. I dessa studier har barn och ungdomar inkluderats, som insjuknade i typ 1 diabetes mellan 1974 och 2021 i ett sjukvårdsdistrikt i södra Sverige, samt unga vuxna med antingen typ 1 eller typ 2 diabetes, som har deltagit i en nationell studie av diabeteskomplikationer, K-DISS, som ingår i Diabetes Incidens Studien i Sverige, DISS.

Resultat:

I. Studien kunde inte påvisa några skillnader i blodsockerkontroll mellan barn och ungdomar med typ 1 diabetes med insulinpumpbehandling jämfört med behandling med insulinpenna. Studien genomfördes i verklig sjukvård, där patienterna och deras vårdnadshavare, tillsammans med diabetesteamet, kunde välja mellan antingen insulinpumpar av olika modell eller insulinpenna, beroende på vilket behandlingshjälpmedel som bedömdes passa bäst i det enskilda fallet. Alla patienter både i pump- och penngruppen hade tillgång till kontinuerlig sockermätning (CGM). Det kan alltså vara så att bruk av CGM är mer betydelsefullt för blodsockerkontrollen än själva sättet att ge insulin, med pump eller penna, om valet är fritt och individuellt anpassat.

II. På sikt löper patienter med typ 1 och typ 2 diabetes risk att utveckla diabeteskomplikationer, till exempel i ögats näthinna. De lösliga ämnena E-selectin, ICAM-1 och VCAM-1 kan analyseras i blodet. Studien visade att lösligt E-selectin möjligen kan förutsäga ögonkomplikationer vid typ 2 diabetes. För lösligt ICAM-1 och VCAM-1, kunde inte några liknande slutsatser dras avseende möjlig förutsägelse vare sig för typ 1 eller typ 2 diabetes.

III. HbA1c är ett mått på långtidsblodsocker. Studien visade att högt HbA1c, dvs ett högre långtidsblodsocker, var förenat med kortare tid till utveckling av ögonkomplikationer. Dessutom visade studien att ju tidigare i livet man diagnostiseras med typ 1 diabetes, desto kortare är tiden till utveckling av ögonkomplikationer.

IV. I det studerade sjukvårdsdistriktet har nyinsjuknandet i typ 1 diabetes bland barn och ungdomar ökat över tid, trots ökad invandring från områden i världen som har lägre förekomst av diabetes.

Slutsatser: Dessa studier bekräftade betydelsen av att hålla blodsockret så normalt som det går för att minska risken för diabeteskomplikationer över tid. Sökandet efter markörer för att kunna förutsäga ögonkomplikationer bör fortsätta med studier på

större patientmaterial, bredare åldersgrupper och med längre uppföljningstid. CGM framstår som betydelsefullt för en god blodsockerkontroll vid såväl insulinpumpbehandling som behandling med insulinpenna. Någon jämförelse av livskvalitetsaspekter mellan pump- och pennbehandling gjordes dock inte i denna studie. Tekniken avseende såväl CGM som insulinpumpar utvecklas i snabb takt. När studien genomfördes så hade endast ett fåtal patienter tillgång till den mer avancerade pumpbehandlingen, automatiserad insulintillförsel, som numera är betydligt vanligare. Nyttan av sådan teknik har därför inte utvärderats i detta arbete.

Abbreviations

AID	Automated insulin delivery
Anti-VEGF	Anti-vascular endothelial growth factor
BMI	Body mass index
CGM	Continuous glucose monitoring
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DISS	Diabetes Incidence Study in Sweden
DR	Diabetic retinopathy
EDIC	Epidemiology of Diabetes Interventions and Complications study
ELISA	Enzyme-linked immunosorbent assay
HbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
ICA	Islet cell antibodies
IFCC	International Federation of Clinical Chemistry
IQR	Interquartile range
JDF	Juvenile Diabetes Foundation
K-DISS	Complications trial of the Diabetes Incidence Study in Sweden
LN	Natural logarithm
MDI	Multiple daily injections
MODY	Maturity-onset diabetes of the young
NDR	The Swedish National Diabetes Register
NGSP	National Glycohemoglobin Standardization Program
r_s	Spearman's rank correlation
SAS	Statistical Analysis System
SD	Standard deviation
sE-selectin	Soluble endothelial selectin
sICAM-1	Soluble intercellular adhesion molecule-1

SQRT	Square root
sVCAM-1	Soluble vascular cell adhesion molecule-1
TITR	Time in tight range
tTG	Tissue transglutaminase
vB-pH	Venous blood pH
vP-glucose	Venous plasma glucose

Background

Epidemiology and characteristics of type 1 diabetes in children and adolescents

Epidemiology

History

Diabetes mellitus has been described since ancient times. Due to previous lack of treatment, the prevalence of the disease has been low. Insulin became available in 1921 and before that, patients with type 1 diabetes had a short survival time. The prevalence of type 1 diabetes was therefore neglectable. During the last 100 years when insulin treatment has been available, an enormous improvement of treatment has led to increased survival and better quality of life for patients with diabetes of all types. Higher survival rate has contributed to an increased prevalence, but lifestyle changes are even more likely to explain the great increase in diabetes incidence observed all over the world.

Incidence, prevalence and geographical variation

Type 1 diabetes is one of the most common chronic diseases diagnosed in childhood. The cause is insulin deficiency as a result of destruction of the insulin producing beta cells in the pancreas. Although most commonly presenting in childhood, around 25% of cases are diagnosed in adults. In recent years, the incidence and prevalence of type 2 diabetes have increased substantially [1]. Diabetes in children and adolescents has traditionally been almost synonymous with type 1 diabetes, which remains the most common form of diabetes in childhood [2, 3]. The incidence of type 1 diabetes with onset during childhood varies in different countries but has increased globally, with Finland noting the highest incidence rate, followed by Sweden [4-8]. According to some studies, the incidence rates of type 1 diabetes in Finland and Sweden have stabilized over the last two decades [4, 9, 10], whereas another study has indicated a continued increase in type 1 diabetes incidence in Sweden, with a rate of 48.8 per 100,000 children under the age of 15 years 2014 to 2015 [11]. An estimate of the incidence rate in 2021 in Sweden by the International Diabetes Federation was 44.1 per 100,000 children under the age of 15 years [7]. The world map in Figure 1 illustrates the estimated incidence rates of type 1 diabetes

in children 0 to 14 years of age until 2018 in certain areas whereas data from many regions in Africa and Asia are not available [6].

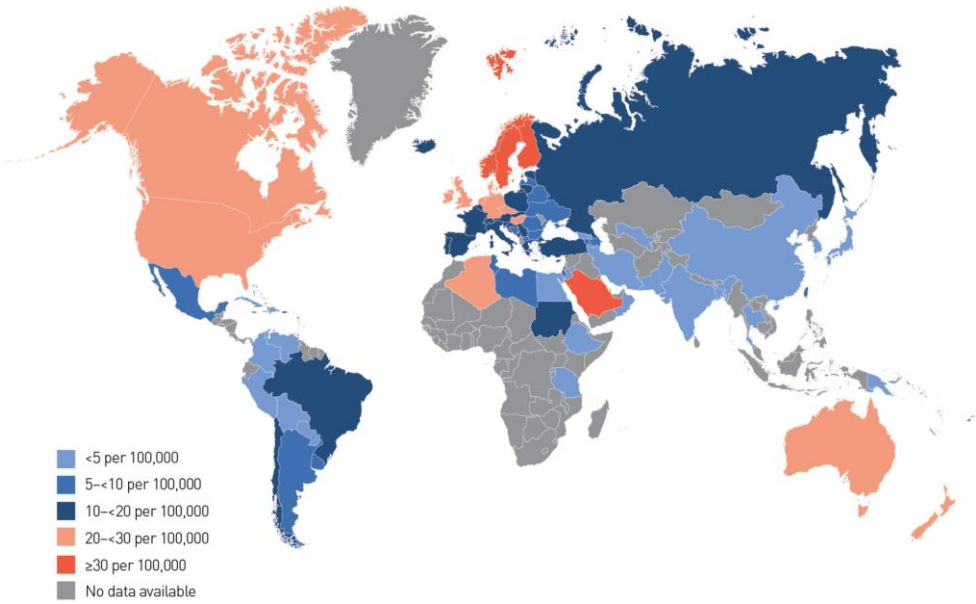

Figure 1. Map illustrating age-sex standardized incidence rates (per 100,000) from publications of type 1 diabetes in children under the age of 15 years [6].
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Age and sex

The age of onset of childhood type 1 diabetes has a bimodal distribution. One peak appears at 4 to 6 years of age, and another one during puberty at 10 to 14 years [12-14]. In total, around 45% of childhood diabetes is diagnosed before the age of 10 years [15]. Type 1 diabetes constitutes almost all cases of diabetes diagnosed under the age of 10, 90% in the age group 10 to 14 years and 80% in the group 15 to 19 years of age [3]. Remaining children with diabetes not having type 1 diabetes, most often have type 2 diabetes. Single cases of maturity-onset diabetes of the young (MODY) or neonatal diabetes are diagnosed but these are exceptional cases [16]. Type 2 diabetes among children has been quite common in the United States, but a similar trend has so far not been observed in Sweden.

Type 1 diabetes is considered an autoimmune disease. Most autoimmune diseases are more common in females but there are no apparent differences in the overall incidence of type 1 diabetes between girls and boys in the pediatric population [2, 3]. However, some studies have showed higher occurrence of type 1 diabetes in

males. Worldwide, the ratio of males to females who have been diagnosed with type 1 diabetes as young adults is around 1.5:1 [17]. This is in alignment with the male to female ratio reported in pediatric patients below the age of 6 years in an observational study from the United States [18].

Time trends

International multicenter studies have reported an increase in the incidence of 3% per year in the age group 0 to 14 years worldwide since the 1980s.The time trends vary among populations within the age groups [19]. In Europe, the most pronounced relative increase in incidence has been noted in children under the age of 5 years [4, 19-24]. In the United States, the increase in incidence has been approximately 2% per year from 2002-2003 to 2014-2015, when the incidence increased from 19.5 to 22.3 per 100,000 [25]. During the same time, the increase in prevalence has been from 1.48 to 2.15 per 1,000 [3]. An increase in incidence, of two to three times what previously has been reported, of type 1 diabetes has been described also in patients between 15 to 34 years of age in Sweden [26, 27].

Pathophysiology and risk factors

Type 1 diabetes is associated with autoantibodies such as islet cell antibodies (ICA), targeting the insulin producing beta cells in the pancreas. These autoantibodies can usually be identified prior to diagnosis of diabetes. The autoimmune process is observed parallel with the destruction of the beta cells. [16]. The autoantibodies are potentially detectable several years prior to the onset of clinically evident diabetes and tend to increase in number at time for diagnosis and will thereafter gradually disappear. Therefore, such autoantibodies can serve as predictors for the development of type 1 diabetes [28-31]. The etiology of type 1 diabetes remains unknown, but a combination of genetic as well as environmental factors are considered important for the development of the disease. On the short arm of chromosome 6 in the Human Leukocyte Antigen (HLA) class II locus, genes influencing susceptibility for type 1 diabetes can be found. The HLA haplotypes DR3-DQ2 and/or DR4-DQ8 can be identified in more than 90% of children with type 1 diabetes [32, 33]. However, the presence of risk genes alone is not enough for development of type 1 diabetes, since only approximately 5% of individuals with such a genetic predisposition will have progressed to clinical disease by the age of 15 [34].

The lifetime risk of developing type 1 diabetes is significantly increased in close family members of a patient with type 1 diabetes [8, 35-37]:

- Without family history – 0.4%
- Affected mother – risk for offspring – 1–4%
- Affected father – risk for offspring – 3–8%
- Both parents affected – risk for offspring – 30% [38, 39]
- Sibling (non-twin) affected – 3–6% by 20 years of age [36] and 10% by 60 years of age [40]
- Dizygotic twin affected – 8%
- Monozygotic twin affected – 30% within 10 years of diagnosis of the first twin and 65% by the age of 60 years [41]

Ethnic differences in the incidence of type 1 diabetes have been reported also from the United States. The highest prevalence per 1000 pediatric patients below 19 years of age was found in non-Hispanic Whites (2.79), followed by Black patients (2.18), Hispanics (1.56), Asian and Pacific Islanders (0.76), and Native Americans (0.56) [3].

The autoimmune process, leading to destruction of the beta cells, and ultimately to the development of type 1 diabetes, is considered to be initiated by various environmental factors and lifestyle habits, which potentially also can contribute to differences in geographical disparities and to the increasing incidence overall [6, 42-44]. It has been hypothesized that viral infections (such as enterovirus, coxsackie B virus, cytomegalovirus, rotavirus, mumps, rubella, and retroviruses), early exposure to cow's milk formula as well as rapid growth and weight gain, are potential risk factors for the development of type 1 diabetes. On the other hand, breastfeeding and early supplementation of vitamin D, have been associated with a lower risk of type 1 diabetes [42-44]. The geographical variation with higher prevalence of type 1 diabetes in northern countries as well as within-country variation, and the seasonal variation with higher incidence during autumn and winter, suggest a potential influence of cold climates and low sun exposure, resulting in low vitamin D levels [22, 45]. Migrant research has indicated that populations moving from low-incidence to high-incidence areas exhibit an increased incidence of type 1 diabetes, emphasizing the role of environmental conditions. Changes in food habits due to migration coincide with the rising incidence of type 1 diabetes in Sweden and may be significant [46]. The hygiene hypothesis is based on the assumption that a lack of exposure to antigens in the environment might lead to increased sensitivity later, and thereby to increased risk of development of autoimmune diseases [47-49]. Environmental changes over recent decades are considered a contributing factor to the increased incidence of

type 1 diabetes, even in people with less genetic susceptibility and at a younger age [40]. Consequently, gaining a deeper understanding of environmental factors and the onset of the disease, holds the potential to enhance prediction, prevention, and medical care for type 1 diabetes.

Clinical presentation

Type 1 diabetes has three initial presentations, relevant for clinical purposes [50]:

- Classic onset
    - Polydipsia – due to increased thirst because of an increase in serum osmolality resulting from hyperglycemia and hypovolemia.
    - Polyuria – due to significant increase in plasma glucose concentration above 10 mmol/L, thereby exceeding the renal threshold for glucose. This leads to increased excretion of glucose in the urine and osmotic diuresis, i.e., polyuria and hypovolemia. This may lead to nocturia, bedwetting and sudden daytime incontinence in a child who previously has been continent. In younger children, caregivers may note unusually wet diapers.
    - Weight loss – due to hypovolemia and increased catabolism. Deficiency of insulin impairs the utilization of glucose in skeletal muscle, resulting in increased breakdown of fat and muscle. The child's appetite is initially increased, but over time thirst becomes more predominant and ketosis causes anorexia and nausea which contribute to weight loss.
    - Hyperglycemia and ketonemia/ketonuria
- Diabetic ketoacidosis
    - The second most common form of presentation for type 1 diabetes. The symptoms are like, but usually more severe, the ones at classic new onset. In addition to those symptoms, patients with ketoacidosis may present with certain neurologic findings such as drowsiness and lethargy and a fruity-smelling breath.
- Asymptomatic and incidental discovery
    - Type 1 diabetes might be diagnosed before onset of symptoms. This might occur in children with a family member with diabetes, by that family member or by a health care professional with high suspicion. Children who are related to patients with type 1 diabetes may also participate in screening programs using genetic markers and

diabetes related autoantibodies for risk estimation of diabetes and early detection of diabetes [51, 52].

Type 1 diabetes is now considered to have four stages [53, 54]:

- Stage 1 – Beta cell autoimmunity with 2 or more islet autoantibodies detectable, with normal plasma glucose and without symptoms
- Stage 2 – Beta cell autoimmunity with 2 or more islet autoantibodies detectable, with abnormal glucose tolerance and usually with absence of symptoms
- Stage 3 – Beta cell autoimmunity and increased plasma glucose above the diagnostic thresholds and usually with symptoms
- Stage 4 – Established/longstanding type 1 diabetes

Approach to diagnosis

There are several types of diabetes, and type 1 diabetes is one of those. Therefore, the initial step is to diagnose diabetes, and the second step is to differentiate type 1 diabetes from other forms of diabetes. This is based on clinical signs and symptoms and laboratory results.

Diabetes mellitus is diagnosed based on one of these four signs of abnormal glucose metabolism [8, 16, 55]:

- Fasting plasma glucose ≥7 mmol/L on more than one occasion
- Random venous plasma glucose ≥11.1 mmol/L together with classic symptoms of hyperglycemia
- Plasma glucose ≥11.1 mmol/L measured 2 hours after intake of 1.75 g glucose/kg (max dose 75 g) = oral glucose tolerance test
- Hemoglobin A1c (HbA1c) ≥48 mmol/mol as per International Federation of Clinical Chemistry (IFCC) or ≥6.5% as per the National Glycohemoglobin Standardization Program (NGSP). This criterion must be confirmed by another measure of hyperglycemia. Importantly, HbA1c is not appropriate for diagnosis of type 1 diabetes due to the delay before HbA1c is increased.

Epidemiology and characteristics of type 2 diabetes in children and adolescents

Epidemiology

In many countries, the incidence of type 2 diabetes in the pediatric population has increased since the early 1990s [1, 56, 57]. This increase is linked to rise in obesity in children. Type 2 diabetes and its comorbidities are risk factors for vascular complications, and premature mortality, later in life [58]. In the United States, the incidence of type 2 diabetes increased sharply from 9.0 cases per 100,000 in 2002-2003 to 13.8 cases per 100,000 in 2014-2015 [25]. Before the 1980s, type 2 diabetes was considered negligible, but since then there has been significant increases in several countries, such as Japan [59], Argentina [60], and other countries [61].

Pathophysiology and risk factors

The glucose homeostasis is maintained by a balance between the insulin sensitivity in the liver, adipose tissue, and skeletal muscle on one hand and insulin secretion from the beta cells on the other. If the sensitivity to insulin declines, this must be compensated by an increase in the insulin secretion in order to maintain the glucose tolerance. In most children and adolescents, such an increase in insulin secretion occurs as compensation for insulin resistance due to obesity, which is an important risk factor for type 2 diabetes, but also for increased insulin resistance due to puberty. Ultimately, the insulin production might fail [62, 63]. When the beta cells no longer can secrete enough insulin to compensate for the insulin resistance, abnormal glucose homeostasis is the result, which potentially can progress to prediabetes and type 2 diabetes [58]. Several studies have shown that approximately 80% of the pancreatic beta cell function has been lost before the diagnosis of type 2 diabetes [62, 63].

In addition to obesity and excess of adipose tissue, which are the most important risk factors for type 2 diabetes [62, 63], genetic susceptibility is also a risk factor. The causes of type 2 diabetes are complex, and a complex interaction of different environmental factors as well as genetic components, more specifically the expression of multiple genes, are believed to play a role [64]. Furthermore, ethnicity plays a role. Type 2 diabetes is more common in African American, Asian American, Hispanic, Native American and Pacific Islander youth than in the general population in the United States [65-75]. Age also plays a role since a physiologic insulin resistance occurs during puberty [76-78]. Studies have also shown that girls are 1.2 to 1.7 times more likely than boys to progress from prediabetes and thereby develop type 2 diabetes during adolescence [15, 25, 68, 75, 79, 80]. Around 40% of type 2 diabetes cases in the pediatric population occur between 10 and 14 years of

age and 60% between 15 and 19 years [15]. During puberty, there is an increased activity of growth hormone, resulting in approximately 30% decrease in insulin sensitivity [81].

Clinical presentation

Approximately 40% of patients in the pediatric population with type 2 diabetes are identified while still being asymptomatic [74, 82], e.g., with a urinalysis as part of a routine physical examination [79].

Around 60% of pediatric patients with type 2 diabetes have symptoms when being diagnosed [74, 82]. The main symptoms are the classic diabetes symptoms due to hyperglycemia, i.e., polyuria, polydipsia and nocturia. Weight loss might also be present, although typically less than in patients with type 1 diabetes [79, 80].

Occasionally, pediatric patients with type 2 diabetes may present with diabetic ketoacidosis. Diabetic ketoacidosis as the reported initial presentation for type 2 diabetes in children and adolescents varies from 5 to 12% depending on the type of population that has been investigated [74, 80, 82-93].

In rare cases, adolescents with type 2 diabetes may present with hyperosmolar hyperglycemic nonketotic syndrome, also known as hyperosmolar hyperglycemic state. This is an acute emergency, characterized by very high glucose levels and hyperosmolality, severe dehydration and little or no ketonuria [94].

Approach to diagnosis

Diagnosing type 2 diabetes follows the same principles as diagnosing type 1 diabetes, with some additional considerations:

Due to the association between overweight/obesity and type 2 diabetes, screening is recommended in patients with body mass index (BMI) $\geq 85^{th}$ percentile and with one or more of the additional risk factors: type 2 diabetes in first- or second-degree relative, member of high-risk racial or ethnic group, history of gestational diabetes or maternal diabetes during the child's gestation, signs of insulin resistance or conditions associated with it or use of weight-promoting medications [58, 95, 96].

HbA1c and/or fasting plasma glucose can be used to screen for asymptomatic type 2 diabetes. [58, 95, 96]. HbA1c is a useful tool for screening in clinical practice since fasting is not needed. However, HbA1c as such a screening tool is not considered fully validated in adolescents. The diagnostic criteria [16, 95] are the same as for adult patients, i.e.:

- Diabetes – HbA1c ≥48 mmol/mol on two occasions
- Prediabetes - HbA1c between 42-47 mmol/mol

Long-term consequences of diabetes

Complications from small and large blood vessels might occur in type 1 diabetes as well as in type 2 diabetes. These micro- and macrovascular complications include retinopathy, nephropathy, peripheral neuropathy, and autonomic neuropathy [96, 97]. Youth with type 2 diabetes have a high prevalence of other associated risk factors for cardiovascular complications. In addition to the diabetes itself, these risk factors include hypertension, obesity, hyperlipidemia, and inflammatory biomarkers [98, 99]. Adults diagnosed early with type 2 diabetes, i.e., between 15 and 30 years of age, have twice as high cardiovascular mortality compared with patients diagnosed with type 1 diabetes of similar duration and age [100]. Due to the increased prevalence of diabetes worldwide, the number of patients with diabetic complications, and hence in need of healthcare to treat these complications, increases [101]. Good metabolic control is key to reduce the risk of complications. In order to reduce the risk of macrovascular complications, intensive treatment of plasma glucose levels, control of hyperlipidemia and hypertension are recommended in pediatric patients with type 2 diabetes [95, 96, 102].

Recommendations for screening and treatment of complications and/or related conditions in type 1 and type 2 diabetes in children and adolescents by the American Diabetes Association are summarized in Table 1 and Table 2.

Table 1. Recommendation for screening and treatment of complications and/or related conditions in **type 1 diabetes** in children and adolescents [96].

	Hypertension	Nephropathy	Neuropathy	Retinopathy	Dyslipidemia	Thyroid disease	Celiac disease
Method	Blood pressure monitoring	Albumin-to-creatinine ratio	Foot exam with pulses, vibration, reflexes, and 10-g monofilament sensation tests	Dilated fundoscopy or retinal photography (in Sweden fundus photography is recommended)	Lipid profile	Thyroid-stimulating hormone; consider antithyroglobulin and antithyroid peroxidase antibodies	IgA tTG if total IgA normal; IgG tTG and deamidated gliadin antibodies if IgA is deficient
When to start screening	At diagnosis	At puberty or ≥10 years, and diabetes duration of 5 years	At puberty or ≥10 years, and diabetes duration of 5 years	At puberty or ≥11 years, and diabetes duration of 3 – 5 years. In Sweden, screening starts at 10 years of age.	Soon after diagnosis, ideally after improved glycemia and ≥2 years of age	Soon after diagnosis	Soon after diagnosis
Frequency of screening	Every visit	Annually if normal. Repeat and confirm in 2 – 3 samples during a 6-month period if abnormal	Annually if normal	Every 2 years if normal. Less frequent examination (every 4 years) can be considered if HbA1c <8% and if ophthalmologist agrees.	If LDL <100mg/dL, repeat at 9 - 11 years old; then, if <100 ml/dL, every 3 years	Every 1 – 2 years if thyroid antibodies are negative; more frequently if symptoms develop or thyroid antibodies are detected	Within 2 years and then at five years after diagnosis, if symptoms develop - sooner
Recommended treatment	Lifestyle modification with added angiotensin converting enzyme inhibitor or angiotensin receptor blocker if needed	Optimization of glycemia and blood pressure. Addition of angiotensin converting enzyme inhibitor if albumin-to-creatinine ratio is elevated in repeat samples over 6 months.	Optimization of glycemia, consider referral to neurologist	Optimization of glycemia, treatment per ophthalmologist	Optimization of glycemia and dietary advice. Consider statins >10 years of age if needed.	Appropriate treatment of the underlying thyroid disorder	Start gluten-free diet after diagnosis has been confirmed

tTG, tissue transglutaminase.

Table 2. Recommendation for screening and treatment of complications and/or related conditions in **type 2 diabetes** in children and adolescents [96].

	Hypertension	Nephropathy	Neuropathy	Retinopathy	Dyslipidemia	Nonalcoholic fatty liver disease	Obstructive sleep apnea	Polycystic ovarian syndrome (adolescent females)
Method	Blood pressure monitoring	Albumin-to-creatinine ratio	Foot exam with pulses, vibration, reflexes, and 10-g monofilament sensation tests	Dilated fundoscopy (in Sweden fundus photography is recommended)	Lipid profile	Transaminases	Screening for symptoms	Screening for symptoms, laboratory evaluation if positive symptoms
When to start screening	At diagnosis	At diagnosis	At diagnosis	At or soon after diagnosis	Soon after diagnosis, ideally after improved glycemia	At diagnosis	At diagnosis	At diagnosis
Frequency of screening	Every visit	Annually if normal. Repeat and confirm in 2 – 3 samples during a 6-month period if abnormal.	Annually if normal	Annually if normal	Annually	Annually	Every visit	Every visit
Recommended treatment	Lifestyle modification with added angiotensin converting enzyme inhibitor or angiotensin receptor blocker if needed	Optimization of glycemia and blood pressure. Addition of angiotensin converting enzyme inhibitor if albumin-to-creatinine ratio is elevated in repeat samples over 6 months.	Optimization of glycemia, consider referral to neurologist	Optimization of glycemia, treatment per ophthalmologist	Optimization of glycemia and dietary advice. Consider statins >10 years of age if needed. Consider fibrates if needed for elevated triglycerides.	Referral gastroenterologist if transaminases are persistently elevated or worsening	If symptoms, refer to sleep specialist and polysomnogram	Consider oral contraceptive pills, metformin, and dietary advice

Retinopathy

Characteristics

Retinopathy is the most common complication associated with diabetes, and most often the first detected complication. This is probably due to the diagnostic method where the retinal vessels can be directly inspected, giving an opportunity to early detection of minor changes. Photo screening is therefore a useful tool to identify patients with increased risk of future progressive and serious complications. Diabetes-associated retinopathy is a progressive condition affecting the microvasculature of the retina. Clinically, diabetic retinopathy is classified and diagnosed according to the following criteria [103-105]:

- **Mild non-proliferative diabetic retinopathy**
    - Retinal findings: only microaneurysms
- **Moderate non-proliferative diabetic retinopathy**
    - Retinal findings: at least one hemorrhage or microaneurysm and/or at least one of the following:
        - Venous beading
        - Hard exudates
        - Cotton wool spots
        - Retinal hemorrhages
- **Severe non-proliferative diabetic retinopathy**
    - Retinal findings: any of the following but no signs of proliferative diabetic retinopathy:
        - Prominent intraretinal microvascular abnormality in at least one quadrant
        - >20 intraretinal hemorrhages in each of the four quadrants
        - Definite venous beading in at least two quadrants
- **Proliferative diabetic retinopathy**
    - Retinal findings: one of either:
        - Vitreous/preretinal hemorrhage
        - Neovascularization

At an early stage, increased vascular permeability and capillary occlusion cause microaneurysms, hemorrhages and hard exudates (Figure 2), which can be detected by fundus photography. The advanced stage is characterized by neovascularization, also showcased in Figure 2. Diabetic macular edema constitutes the most common cause of vision loss in patients with retinopathy [106, 107]. Importantly, retinopathy is treatable and hence regularly performed fundus photography should be performed according to treatment guidelines. Children and adolescents with type 1 diabetes should start screening from the age of 10 years and patients with type 2 diabetes already from diagnosis of diabetes [97, 105].

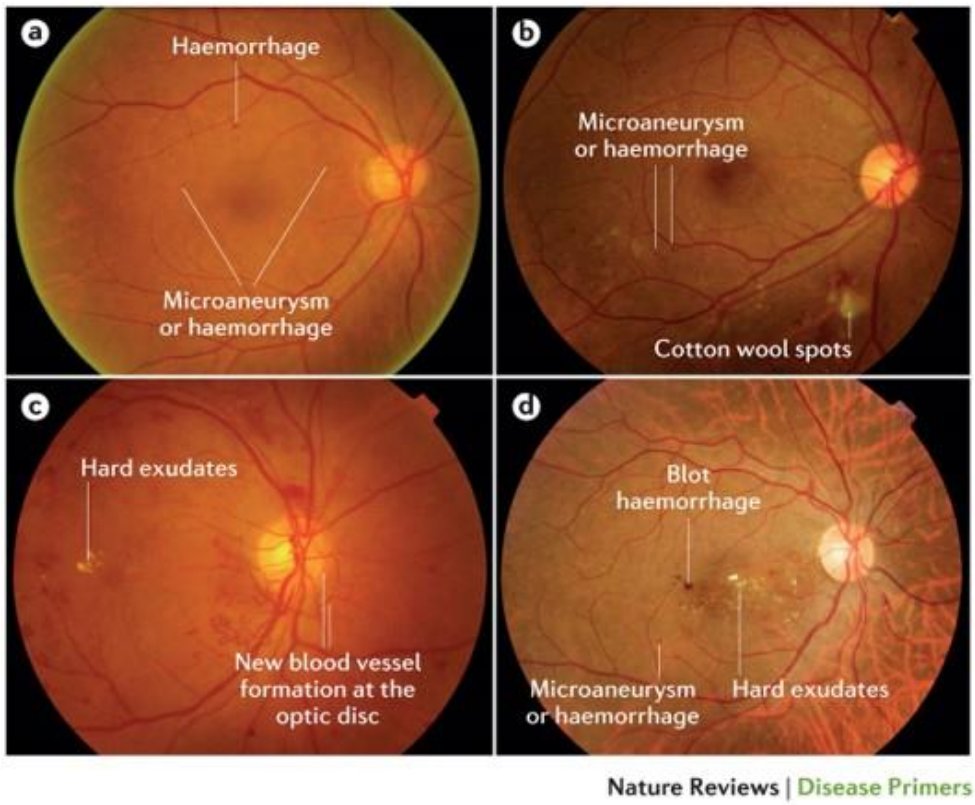

Figure 2. Clinical signs of diabetic retinopathy [108].
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Suboptimal glycemic control, long diabetes duration, uncontrolled hypertension, dyslipidemia, puberty, pregnancy, and certain ethnic origins, are important risk factors for development and progression of diabetic retinopathy [106, 109-114]. However, findings regarding sex and BMI have been inconsistent [112, 115-119].

The prevalence of retinopathy among adolescents and young adults with type 1 has been reported as 5.6%, in the SEARCH study [120], and as 3.4%, in a more recent study [121]. The declining trend over time for retinopathy in patients with type 1 diabetes can be attributed to intensive diabetes treatment with better glycemic control [122].

Prediction of diabetic retinopathy

Since retinopathy is treatable, and since early detection and treatment is important, identification of potential predictors for the development of retinopathy, would be of value. The prevalence of retinopathy is significant, with about a third of patients with diabetes showing signs of retinopathy, and with an even higher prevalence of retinopathy in type 1 diabetes, which can lead to impaired or lost vision [106, 112]. There is also a concern that the prevalence of type 2 diabetes and retinopathy increases. With a mean diabetes duration of 11 years in adolescents and young adults with type 2 diabetes, the TODAY follow-up study reported an increase in prevalence of retinopathy to 51.0% in 2017 to 2018 compared to 13.7% seven years earlier [114].

The most important thing about identifying individuals with retinopathy is that these subjects constitute a group with increased risk of other more serious complications affecting kidney function and the cardiovascular system.

Circulating biomarkers of inflammation and endothelial dysfunction might have predictive value for the development of retinopathy [123, 124]. It has been shown that hyperglycemia enhances the adhesion of leucocytes to the endothelium via upregulation of certain adhesion molecules, e.g., soluble endothelial selectin (sE-selectin), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) [125, 126]. Such inflammatory activity and endothelial dysfunction, causing increased vascular permeability and destruction of the blood retinal barrier, are considered of importance in the pathogenesis of retinopathy [127, 128]. Soluble forms of adhesion molecules released by the affected endothelium and known to be relevant early in the development of retinopathy, are detectable in plasma [129, 130]. Since these adhesion molecules can be detected in plasma, and since increased expression of sE-selectin, sICAM-1, and sVCAM-1 have been found in patients with type 1 and type 2 diabetes and retinopathy [123, 131-138], although other studies have shown a negative correlation [139-141], it is of interest to evaluate these molecules as potential predictors for the development of diabetic retinopathy.

If a biomarker could be identified for the prediction of retinopathy, it could potentially be used at an early stage for identification of patients with high-risk of developing retinopathy. Healthcare can then be individualized with resources and screening programs focusing on patients with the most urgent needs. Some biomarkers relevant to diabetic retinopathy are listed in Table 3.

Table 3. Inflammatory biomarkers of diabetic retinopathy [129].

Inflammatory biomarker group	Examples
Vascular adhesion molecules	E-selectin, ICAM-1, VCAM-1, sVAP
Cytokines	
Inflammatory	TNFα, IL (1α, 1β, 6, 8), HMGB1
Anti-inflammatory	IL-10
Chemokines	
Pro-inflammatory / angiogenic	MCP-1, MIF, SDF-1, fractalkine
Anti-inflammatory / antiangiogenic	IP10, MIG
Transcription factors	HIF-1, NF-κB
Growth-/angiogenesis-related	
Pro-inflammatory / angiogenic	VEGF, PGF, IGF1, CTGF, stem cell factor
Anti-inflammatory / antiangiogenic	PEDF
Anti-inflammatory / proangiogenic	EPO
Innate immune response cells	Retinal endothelial cells with toll-like receptors

CTGF, connective tissue growth factor; EPO, erythropoietin; HIF-1, hypoxia-inducible factor 1; HMGB1, high-mobility group box 1; ICAM-1, intercellular adhesion molecule; IGF1, insulin-like growth factor ; IL, interleukin; IP10, interferon gamma-induced protein 10; MCP-1, monocyte chemotactic protein 1; MIF, macrophage migration inhibitory factor; MIG, monokine induced by gamma interferon; NF-κB, nuclear factor kappa B; PEDF, pigment epithelium-derived factor; PGF, placental growth factor; SDF1, stromal cell-derived factor 1; sVAP, soluble vascular adhesion protein 1; TNFα, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor.

Treatment

The goals of treatment of diabetic retinopathy include preservation of vision, improvement of vision, and reduction of progression rate and frequency of the condition as well as reduction of vitreous hemorrhage and macular edema [97]. Laser photo coagulation became available in Sweden around 1960 and is an effective treatment option for vision-threatening retinopathy [108, 142, 143]. However, eventually laser photo coagulation leads to damage of retinal receptors and diminished night- and color vision. Retinal scars can give rise to partial loss in the field of vision, which can be an obstacle to retain driving license [144]. Nowadays, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents are recommended as initial therapy, especially for macular edema [105, 107, 145]. In a meta-analysis, such treatment has been shown to increase the chances of improved vision and to decrease the risk of worsened vision, compared to other treatments such as grid laser photocoagulation [146, 147].

Nephropathy

Diabetes-associated nephropathy is a progressive condition affecting the microvasculature of the kidney. The first sign of nephropathy is moderately

increased albuminuria, which previously was referred to as microalbuminuria, presence of which in youth with diabetes is a predictor of progression to overt proteinuria. Overt proteinuria can be accompanied by hypertension and also by impaired glomerular filtration [148]. Risk factors for the development of nephropathy are smoking, chronic hyperglycemia and hypertension. Careful treatment of these risk factors is therefore essential to reduce the risk of nephropathy [148].

Treatment of type 1 diabetes – yesterday, today, and tomorrow

So far, type 1 diabetes can neither be prevented nor cured. Insulin, which now have been available to patients with type 1 diabetes for 100 years, therefore remains the essential replacement treatment for every patient with type 1 diabetes. Insulin has a narrow therapeutic spectrum. Glycemic control as close to normal as possible is crucial for lowering the risk of diabetic complications in the long run, whereas such near normal glycemic values balance close to, potentially serious, hypoglycemic events [149]. In recent decades, insulin analogues have been developed, making a more tailor-made insulin treatment possible for patients treated with multiple daily injections (MDI), often referred to as pen-treatment. Long-acting insulin analogues, with a flatter and more long-acting profile than previous insulins, give a stable basic control of glucose. In combination with rapid acting insulin analogues administered at mealtimes, a more physiological insulin administration is enabled. Insulins with different profiles are nowadays available on the market [150].

The use of continuous subcutaneous insulin infusion (CSII), often referred to as "pump treatment", is often considered an attractive alternative to MDI in type 1 diabetes – in children as well as in adults [96, 151]. Previous studies, where a comparison has been made between MDI and CSII, an association, in favor of CSII, has been found between improved glycemic control and a lower risk of severe hypoglycemia [152-155]. In parallel with the development of even more advanced insulin pumps, the development of continuous glucose monitoring (CGM) in interstitial fluid, has enabled more advanced and, at least partially, automated insulin delivery (AID). An advanced insulin pump and a CGM device work together with a mathematical algorithm that uses real-time glucose data from the CGM to control the delivery of insulin from the insulin pump [156, 157]. CGM therefore constitutes an essential component of such AID systems. Importantly, CGM is also a valuable tool in MDI [149, 154, 157-161].

In Sweden, all types of diabetes treatment for children and adolescents are fully reimbursed. Furthermore, in recent years, the use of CGM in these age groups has become nearly universal in Sweden – 98.6% in 2022 according to the national

registry, in CSII and MDI [162]. Therefore, Sweden might offer an ideal setting to compare glycemic outcomes in CSII versus MDI in the pediatric population with type 1 diabetes.

Aims

The aims of the present work were to study children and adolescents in a district in southern Sweden who were diagnosed with type 1 diabetes between 1974 and 2021, and young adults with either type 1 or type 2 diabetes, participating in the national complications trial of the Diabetes Incidence Study in Sweden (K-DISS).

The specific aims of the individual studies are given below.

I. To ascertain whether the glycemic outcomes in CSII compared to MDI differed in all incident type 1 diabetes patients <18 years of age at diabetes diagnosis during 2015 to 2021 with universal use of CGM in both groups.

II. To determine plasma levels of three adhesion molecules that may contribute to the development of diabetic retinopathy: sE-selectin, sICAM-1, and sVCAM-1, in young adults, aged 15 to 34 years at diagnosis of diabetes, to find potential predictors for development of retinopathy, and to evaluate their relation to diabetes related autoantibodies, in the K-DISS cohort.

III. To investigate if clinical and laboratory characteristics at diagnosis of childhood type 1 diabetes differed between those who had developed diabetic retinopathy 15 years after diagnosis and those who had not and if mean HbA1c levels affect time to development of retinopathy.

IV. To identify potential variations in demographic and disease related factors between childhood type 1 diabetes with onset during a period with lower incidence compared to a period with higher incidence and to calculate the trend in incidence rate 1974 to 2013.

Methods

Paper I

Subjects and study design

The study was conducted as a retrospective observational study at the Department of Pediatrics, Helsingborg Hospital, Sweden. The study population consisted of all children and adolescents <18 years of age diagnosed with type 1 diabetes between January 1, 2015, and September 14, 2021. Data were collected from medical records and from glucose profiles (Diasend®), which provided the information from the CGM used by all participants for monitoring of glucose in interstitial fluid. MDI as well as CSII were used for insulin treatment. Since this was an observational study, the participants could switch from MDI to CSII and vice versa during the study if they wanted. Several types of insulin pumps were used for CSII such as sensor augmented pumps and sensor augmented pumps with sensor based CGM with predictive low glucose suspend function. During the latter part of the follow-up period, pump models with AID functionality had become available and prescribed to some participants.

Initially, 161 children and adolescents were included in the study. Two of them declined to participate and 11 participants were excluded due to no follow-up data since they were diagnosed less than 1 year before the study was closed. Another 5 participants had moved to the studied area, some from abroad, several years after diabetes diagnosis and hence, data were missing. Data from a total of 143 participants were included in the descriptive statistics and the analyses. The duration of the follow-up extended from time of diagnosis until March 23, 2022, encompassing a span of up to 6 years, during which HbA1c, mean sensor glucose and standard deviation (SD) mean sensor glucose (mean value over 3 months prior to measurement time), time in tight range (TITR) 4-8 mmol/L, sensor time <4 mmol/L, and sensor time >8 mmol/L (measured as percentage (%) of CGM readings and time per day over 3 months prior to measurement time) were examined at intervals as close as possible to 1 year. The use of CGM was measured as the aggregated time with sensor in percentage (%) over 3 months preceding each annual reading. The HbA1c values were converted from IFCC (mmol/mol) to NSGP (%) using the tool provided by NGSP [163].

The study population was divided into the two treatment groups MDI and CSII. All participants started with MDI at diabetes diagnosis and if CSII was preferred, the participants switched during follow-up. A few participants switched to CSII and then back to MDI. To obtain groups where treatment was consistent over time, data were censored for the time points that derived from the main treatment. The starting point was the type of treatment the participants had at the end date of the follow-up period.

Statistical analyses

Continuous variables are presented as mean, SD, median, minimum, and maximum values. Results not normally distributed are presented as median and interquartile range and the Mann-Whitney U test was used for comparison between groups. Categorical variables are presented as proportions. A linear mixed model performed with SAS Proc Mixed was used to estimate the overall differences in outcomes between CSII users and MDI users. The dependence between repeated measures was modelled using an autoregressive covariance structure, AR(1). The estimated overall differences are adjusted for time of measurement, age at diagnosis, sex and HbA1c at diagnosis (also in analyses of outcomes other than HbA1c). An alternative specification adjusts for time-varying BMI, in addition to the covariates mentioned above. To fulfil the assumption of normality, some variables were transformed by the natural logarithm (LN) or square root (SQRT). A p-value of 0.05 was used to determine statistical significance.

Paper II

Subjects and study design

The Diabetes Incidence Study in Sweden (DISS) is a nationwide population-based prospective study which since 1983 registers the incidence of diabetes, as well as diabetes complications, in patients 15 to 34 years of age, aiming at identifying factors that are relevant for the development of diabetes as well as for its complication. Gestational diabetes is not registered [164]. K-DISS is a sub study of DISS, focusing on diabetes complications, from which data have been used to investigate the prevalence of diabetic retinopathy, and part of those results were used in the study presented in Paper II [115].

The population of the present study consisted of all patients participating in K-DISS, diagnosed by physicians as having either type 1 diabetes or type 2 diabetes. The inclusion was performed in 1987 to 1988 with the participants then being 15 to 34 years old. In order not to risk including patients potentially having nephropathy by

another etiology than diabetes, participants who developed either nephropathy or the combination of nephropathy and diabetic retinopathy during follow-up were excluded. The process to include patients in the study is visualized in Figure 3.

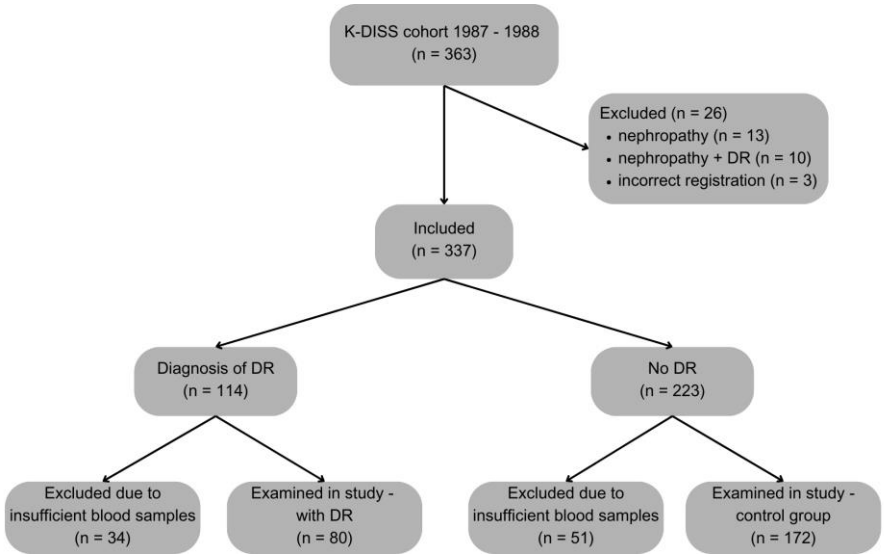

Figure 3. The recruitment process of the study participants.
K-DISS, complications trial of the Diabetes Incidence Study in Sweden; DR, diabetic retinopathy.

When follow-up was performed 8 to 10 years after diabetes had been diagnosed, 114 out of 337 participants had developed diabetic retinopathy to any degree, but no other diabetes complications. The control group was formed by the remaining 223 participants in the study, i.e., without retinopathy or any other diabetes complications. Some blood samples contained insufficient volume of blood for the tests to be conducted and finally, 80 participants in the group with retinopathy and 172 participants in the control group were examined.

In most cases, diabetic retinopathy was classified by performing dilated retinal photography. If no retinal photographs had been taken, the classification was performed by ophthalmoscopy or by slit-lamp bio-microscopy data from medical records, and the 11-step scale of alternative classification of the Wisconsin study [115, 165] The median number of eye examinations by photography was three per participant, without differences between type 1 and type 2 diabetes. Central assessment of all photographs taken since diabetes diagnosis, was conducted by two experienced and independent assessors. The eye most severely affected was considered index eye and used to determine the severity of retinopathy.

Laboratory analyses

At diagnosis of diabetes, blood samples were collected and sent to the central laboratory at Malmö General Hospital for analyses. Plasma was separated by centrifugation at 2000 x g and stored in a freezer at a temperature of -80º C until the analyses of the adhesion molecules were performed. ICA were determined, in serum samples collected at diagnosis of diabetes, by a prolonged two-color immunofluorescent assay [166, 167]. HbA1c was measured at local laboratories using ion-exchange chromatography. All HbA1c values since diagnosis were requested and the mean HbA1c value during the entire follow-up period was calculated for each participant.

Determination of the plasma concentrations of the soluble adhesion molecules were performed by using the enzyme-linked immunosorbent assay ELISA DuoSet (R&D Systems, Minneapolis, MN, USA) (Figure 4). The instructions from the manufacturer were followed. Plasma samples were diluted 1:25 for sE-selectin, 1:200 for sICAM-1, and 1:1000 for sVCAM-1. Samples from participants with and without retinopathy were alternated on each ELISA microplate to reduce interassay variability and measured in duplicate. For absorbance measurements at 450 nm and 580 nm, a FLUOstar Optima Microplate Reader (BMG LABTECH, Ortenberg, Germany) was used. A four-parametric logistic regression standard curve was used to calculate the concentrations.

Figure 4. Photographs from the Diabetes Research Laboratory, BMC, Lund, taken by the author at the time when the author also conducted the laboratory analyses.
VCAM-1, vascular cell adhesion molecule-1.

Statistical analyses

Every HbA1c value available since diagnosis of diabetes was used to calculate the mean HbA1c by using the area under the curve of HbA1c over time to compensate for the occasionally irregular intervals between the different measurements.

The D'Agostino-Pearson test was used to examine normal distribution of data. Results that were normally distributed are presented as mean ± SD. The t-test was used for comparison between groups. The non-parametric variables, i.e., results not normally distributed, are presented as median and interquartile range and the Mann-Whitney U test was used for comparison between groups. Frequencies are presented as numbers and percentages and were compared using the chi-squared test. Correlations between variables were determined using Spearman's rank correlation (r_s) test and presented with 95% confidence intervals (CI). Logistic regression was used to analyze the effect of several independent variables on retinopathy. Only statistically significant variables were included in a multivariate analysis model. P-values below 0.05 were considered statistically significant.

Paper III

Subjects and study design

In this retrospective study, children and adolescents <18 years of age diagnosed with type 1 diabetes between 1993 and 2001 in the district of Helsingborg and Ängelholm, located in southern Sweden, were included. In total, 108 children and adolescents were diagnosed, and all chose to participate. 36 participants were excluded; 7 had missing medical records at time of diagnosis, 19 had incomplete HbA1c data, 7 moved out of the region, and 3 were diagnosed with type 2 diabetes. Consequently, 72 participants were included, and the follow-up period extended from 15 to 23 years from time of diabetes diagnosis.

Data from medical records were analyzed regarding the onset of type 1 diabetes and sex, age at diabetes diagnosis, weight loss prior to diagnosis, weight at admission to hospital, weight at discharge from hospital, blood pressure, venous plasma glucose (vP-glucose), HbA1c, C-peptide, venous blood pH (vB-pH), base excess, ketoacidosis (pH < 7.30, base excess < -6) at diagnosis, family history of diabetes, ethnicity, and parental separation. Previously, HbA1c values in Sweden were reported as Mono S. In 2011, the standard was changed to IFCC. Therefore, Mono S values were converted to IFCC values using the formula: [HbA1c, IFCC, mmol/mol] = 10.45 x [HbA1c, Mono S, %] – 10.62 [168, 169].

Up to four HbA1c values per participant per year were recorded, and an annual mean value was calculated until manifest mild NDPR was diagnosed. The ophthalmic

clinic at Helsingborg Hospital used the Wisconsin Epidemiologic Study of Diabetic Retinopathy severity scale to classify the progression of diabetic retinopathy [170].

Statistical analyses

The D'Agostino-Pearson test was used to examine normal distribution of data. Results that were normally distributed are presented as mean ± SD. The t-test was used for comparison between groups. Results not normally distributed are presented as median and minimum to maximum and the Mann-Whitney U test was used for comparison between groups. Frequencies are presented as numbers and percentages and were compared using the chi-squared test. Correlations between variables were determined using Pearson's correlation test or Spearman's rank correlation (r_s) test and presented with 95% CI. The Kaplan-Meier survival analysis, which illustrates a time-to-event model, was used to estimate the time from diabetes diagnosis until development of retinopathy. The coefficient of variation was used to describe variation of HbA1c over time. P-values below 0.05 were considered statistically significant.

Paper IV

Subjects and study design

The study was performed as a retrospective observational study. Data collected from medical records of 48 children and adolescents <18 years of age with onset of type 1 diabetes between January 1, 1993, and December 31, 1998, were compared to data from 51 children and adolescents <18years of age diagnosed between January 1, 2011, and December 31, 2013. The data were sourced from a local registry and medical records at the Department of Pediatrics at Helsingborg Hospital in southern Sweden. The local registry, established in 1974, initially only recorded incidence until 1991. Subsequently, it incorporated full personal identification, facilitating inclusion in this study. Except for missing data from 1992, the registry is complete. The 48 patients registered from 1993 to 1998 were the initial entries with personal identification, while the 51 patients registered from 2011 to 2013 were the latest entries included in the trial. This study design allowed for a maximum time interval between the two groups, optimizing the potential to identify differences. Three patients from the 1990s were not included due to missing data, whereas all patients from the latter group were included.

Data were analyzed regarding the onset of type 1 diabetes and sex, age at diabetes diagnosis, duration of symptoms, weight loss prior to diagnosis, weight and height at admission to hospital, BMI, weight at discharge from hospital, blood pressure,

vP-glucose, HbA1c, C-peptide, vB-pH, base excess, ketoacidosis (pH < 7.30, base excess < -6) at diagnosis, initial use of intensive care, associated diseases like thyroid gland disorders and celiac disease, diabetes related autoantibodies, HLA-associated genetic diabetes risk and family history of diabetes but also factors such as ethnicity, parental separation and patients' use of alcohol and smoking. The incidence rate of diagnosed type 1 diabetes by years was calculated as an average of three years at a time from 1974 to 2013 except for 1992 due to missing data. Vital population statistics, for children and adolescents younger than 18 years, required for these calculations were found on the website of Statistics Sweden [171].

Statistical analyses

The D'Agostino-Pearson test was used to examine normal distribution of data. Results that were normally distributed are presented as mean ± SD. The t-test was used for comparison between groups. Results not normally distributed are presented as median and interquartile range and the Mann-Whitney U test was used for comparison between groups. Frequencies are presented as numbers and percentages and were compared using the chi-squared test or, in case of small numbers, Fisher's exact test. A Poisson regression model was used to assess the effect of time (year) on the incidence rate of type 1 diabetes. Testing for trend was conducted by fitting three-year periods as a continuous variable in the log-linear Poisson regression model with person-years as an offset. Predicted incidence and 95% CI are presented. P-values below 0.05 were considered statistically significant.

Results

Paper I

The study population of 143 participants consisted of 80 males and 63 females and was divided into the two treatment groups CSII and MDI (Table 4 and Table 5). Among the excluded participants, 12 were males and 6 were females. Depending on year of diabetes diagnosis, 1 to 6 data points per participant were available during the follow-up period for HbA1c, mean sensor glucose, SD mean sensor glucose, TITR, time in hypoglycemia, time in hyperglycemia and time with sensor, respectively.

Table 4. Descriptive statistics for the treatment group CSII.

Characteristics	Mean	SD	Median (IQR)	Minimum	Maximum	Observations
Male (%)	50.6					
Age (years)*	7.8	4.2	8.0	0.86	16.4	79
Weight (kg)*	28.6	15.4	26.1	8.2	72.5	79
Height (m)*	1.30	0.27	1.37	0.71	1.78	55
BMI (kg/m^2)*	16.8	3.7	15.6	12.7	29.2	55
HbA1c IFCC (mmol/mol)*	84.3	23.3	85.0	39.0	154.0	79
HbA1c NGSP (%)*	9.9	2.13	9.9	5.7	16.2	79
C-peptide (nmol/L)*	0.33	0.26	0.25	0.080	1.30	76
Diabetes duration (years)†	3.9	1.8	3.8	0.85	7.3	79
CGM duration (years)†	3.9	1.8	3.8	0.83	6.9	79
HbA1c IFCC (mmol/mol)‡	52.3	9.3	50.4	40.0	102.7	76
HbA1c NGSP (%)‡	6.9	0.85	6.8	5.8	11.6	76
Mean sensor glucose (mmol/L)‡	8.8	1.3	8.6	7.0	14.7	77
SD mean sensor glucose (mmol/L)‡	3.4	0.67	3.4	2.3	5.2	77
TITR 4-8 mmol/L (%)‡	44.8	13.2	44.3	9.0	81.0	77
Sensor time <4 mmol/L (%)‡	5.2	4.2	4.3	0.0	22.5	77
Sensor time >8 mmol/L (%)‡	50.0	14.8	50.8	12.0	91.0	77
Time with sensor (%)‡	88.5	17.0	96.0 (89.5-98.0)	21.0	99.0	77

* At time of diabetes diagnosis.
† At end of follow-up period.
‡ 1 to 6 measurements per individual during the follow-up period.
The data are presented as mean, SD, median, minimum and maximum values, or number (proportion).
CSII, continuous subcutaneous insulin infusion; IFCC, International Federation of Clinical Chemistry; NGSP, National Glycohemoglobin Standardization Program; CGM, continuous glucose monitoring; SD, standard deviation; TITR, time in tight range; IQR, interquartile range.

Table 5. Descriptive statistics for the treatment group MDI.

Characteristics	Mean	SD	Median (IQR)	Minimum	Maximum	Observations
Male (%)	62.5					
Age (years)*	10.5	3.8	11.4	2.2	16.7	64
Weight (kg)*	40.0	20.0	34.8	11.7	104.7	64
Height (m)*	1.46	0.24	1.49	0.84	1.95	57
BMI (kg/m^2)*	17.9	4.6	16.7	12.8	37.9	57
HbA1c IFCC (mmol/mol)*	81.8	27.0	82.0	37.9	151.0	64
HbA1c NGSP (%)*	9.6	2.47	9.7	5.6	16.0	64
C-peptide (nmol/L)*	0.52	0.42	0.42	0.10	1.80	62
Diabetes duration (years)†	3.4	1.7	3.2	0.89	7.2	64
CGM duration (years)†	3.4	1.7	3.2	0.84	7.1	64
HbA1c IFCC (mmol/mol)‡	51.9	9.9	49.3	37.0	78.0	59
HbA1c NGSP (%)‡	6.9	0.91	6.7	5.5	9.3	59
Mean sensor glucose (mmol/L)‡	8.6	1.3	8.4	6.7	12.7	61
SD mean sensor glucose (mmol/L)‡	3.1	0.91	3.0	1.3	5.8	61
TITR 4-8 mmol/L (%)‡	49.3	16.1	48.0	12.5	91.5	61
Sensor time <4 mmol/L (%)‡	4.1	3.9	2.5	0.0	16.3	61
Sensor time >8 mmol/L (%)‡	46.5	15.7	46.0	7.5	86.5	61
Time with sensor (%)‡	85.3	17.8	93.5 (75.2-97.5)	12.0	99.0	61

* At time of diabetes diagnosis.

† At end of follow-up period.

‡ 1 to 6 measurements per individual during the follow-up period.

The data are presented as mean, SD, median, minimum and maximum values, or number (proportion).

MDI, multiple daily injections; IFCC, International Federation of Clinical Chemistry; NGSP, National Glycohemoglobin Standardization Program; CGM, continuous glucose monitoring; SD, standard deviation; TITR, time in tight range; IQR, interquartile range.

No statistically significant differences were found between the groups (CSII vs. MDI) regarding HbA1c ($p = 0.836$), mean sensor glucose ($p = 0.364$), LN transformed SD mean sensor glucose ($p = 0.061$), TITR ($p = 0.216$), SQRT transformed time in hypoglycemia ($p = 0.921$), and time in hyperglycemia ($p = 0.275$), when adjusted for time of measurement, HbA1c at diagnosis, age at diagnosis, and sex (Table 6). HbA1c at diagnosis was included as a covariate even when the outcomes were mean sensor glucose, LN transformed SD mean sensor glucose, TITR, SQRT transformed time in hypoglycemia, and time in hyperglycemia since HbA1c and these parameters are strongly correlated. An alternative specification adjusted for time-varying BMI, in addition to the covariates mentioned above, without statistically significant differences between the groups (CSII vs. MDI) except for LN transformed SD mean sensor glucose ($\beta = 0.098$ [95% CI: (0.00051–0.20)], 289 observations and 126 individuals; $p = 0.049$). P-values are reported without adjustment for BMI to increase the number of observations and individuals.

Table 6. Results linear mixed model CSII vs. MDI.

Outcome	HbA1c IFCC (mmol/mol)	Mean sensor glucose (mmol/L)	SD mean sensor glucose (mmol/L), LN transformed values	TITR 4-8 mmol/L (%)	Sensor time <4 mmol/L (%), SQRT transformed values	Sensor time >8 mmol/L (%)
β (difference CSII-MDI)	0.36	0.22	0.085	-3.4	0.016	3.1
95% CI	(-3.09 – 3.81)	(-0.26 – 0.69)	(-0.0041 – 0.17)	(-8.7 – 2.0)	(-0.31 – 0.35)	(-2.5 – 8.7)
P-value	0.836	0.364	0.061	0.216	0.921	0.275
Observations	361	335	335	335	335	335
Number of individuals	135	138	138	138	138	138

The estimated overall differences are adjusted for time of measurement, age at diagnosis, sex, and HbA1c at diagnosis.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; CI, confidence interval; IFCC, International Federation of Clinical Chemistry; SD, standard deviation; LN, natural logarithm; TITR, time in tight range; SQRT, square root.

Figure 5 illustrates HbA1c, mean sensor glucose, TITR, time in hypoglycemia, and time in hyperglycemia in CSII users and MDI users.

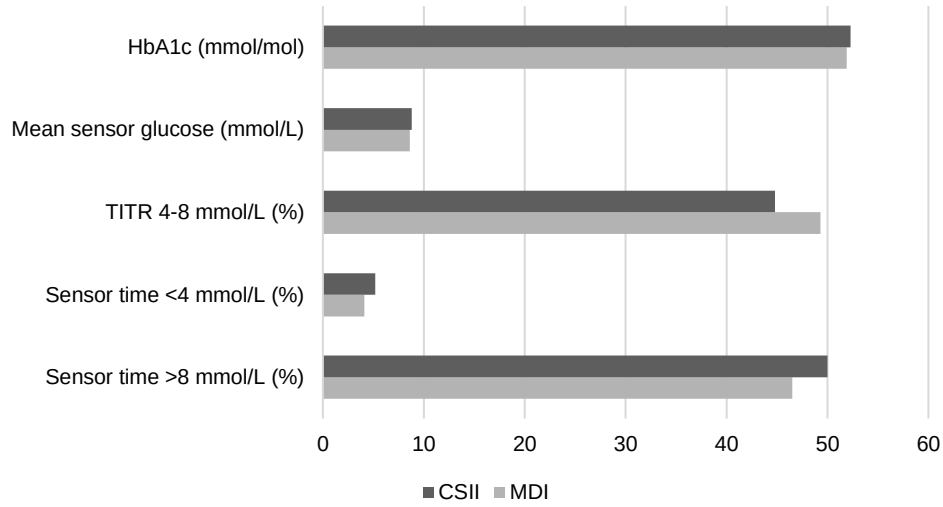

Figure 5. HbA1c (p = 0.836), mean sensor glucose (p = 0.364), TITR (p = 0.216), time in hypoglycemia (p = 0.921), and time in hyperglycemia (p = 0.275) in CSII users and MDI users.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; TITR, time in tight range.

Figure 6-9 present the outcome variables in further detail and the mean time with sensor over time and per group (CSII vs. MDI). CGM usage, expressed as time with sensor, showed no significant difference between the CSII users and MDI users (p = 0.246).

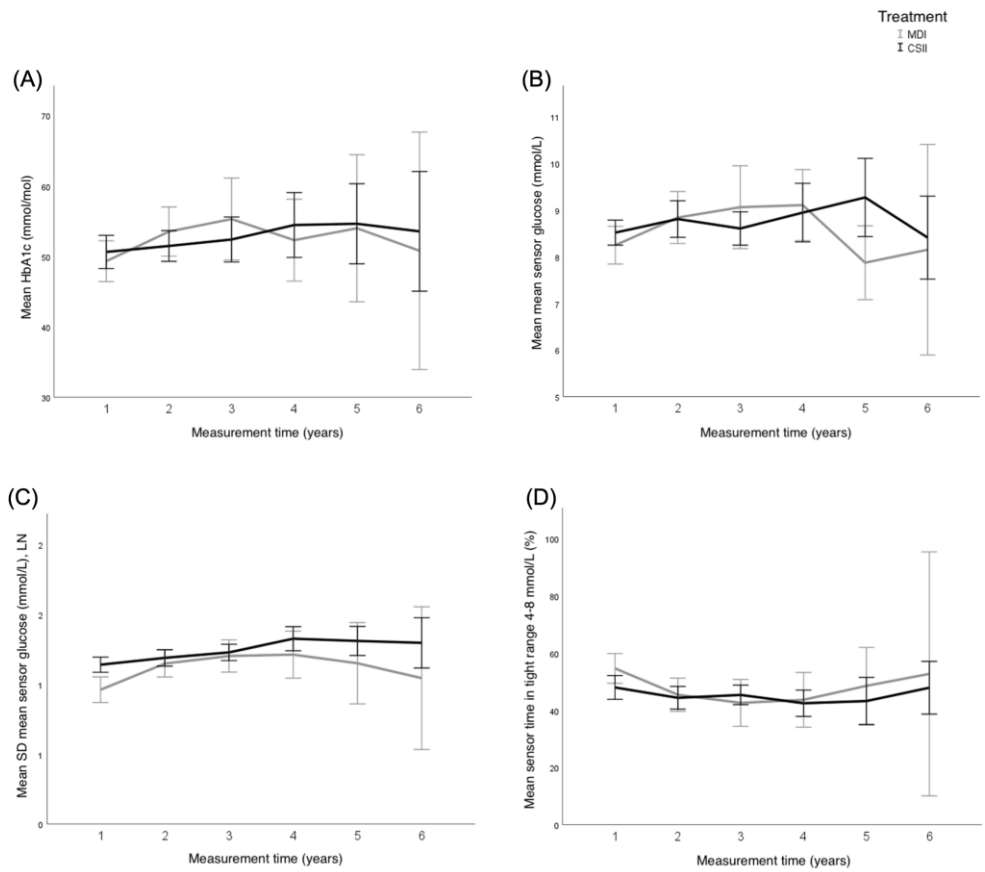

Figure 6. Outcome variables over time and per group (CSII vs. MDI).
(A) Mean HbA1c, p = 0.836; (B) mean mean sensor glucose, p = 0.364; (C) LN transformed mean SD mean sensor glucose, p = 0.061; and (D) mean sensor time in tight range, p = 0.216, over time (years) and per group (CSII vs. MDI). P-values are obtained from the linear mixed model.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SD, standard deviation; LN, natural logarithm.

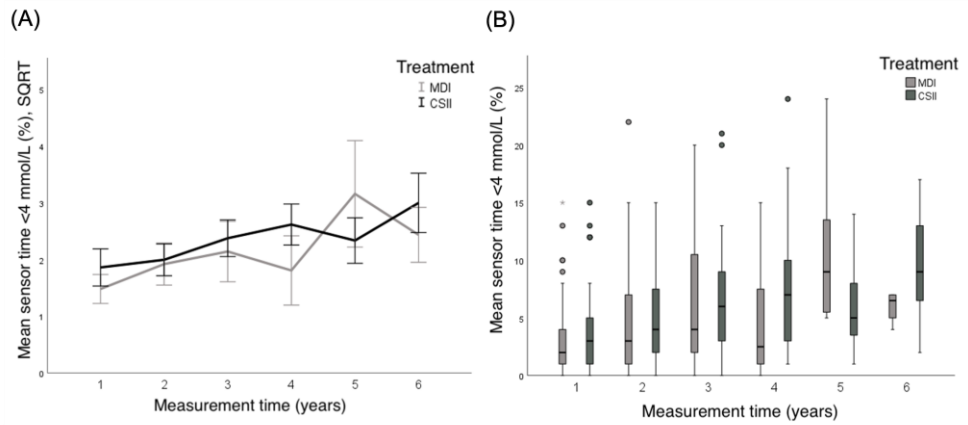

Figure 7. Time in **hypoglycemia** over time and per group (CSII vs. MDI).
(A) SQRT transformed mean sensor time <4 mmol/L; and (B) boxplot of mean sensor time <4 mmol/L, p = 0.921, over time (years) and per group (CSII vs. MDI). P-value is obtained from the linear mixed model.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SQRT, square root.

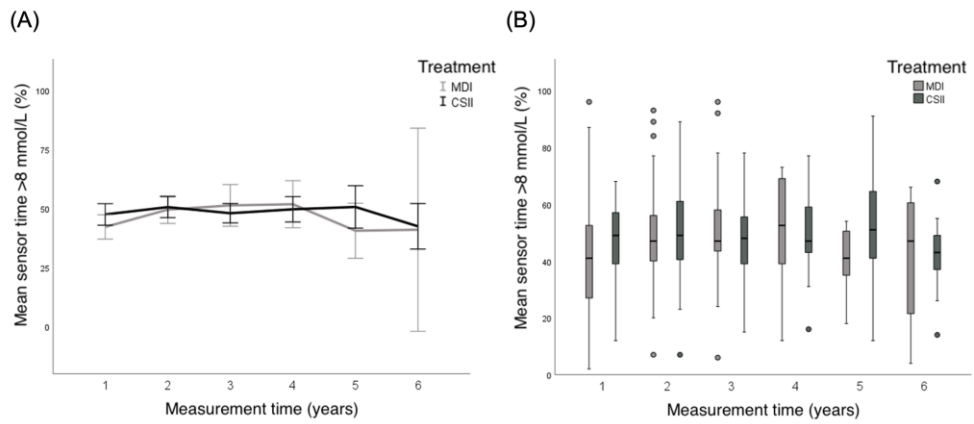

Figure 8. Time in **hyperglycemia** over time and per group (CSII vs. MDI).
(A) mean sensor time >8 mmol/L; and (B) boxplot of mean sensor time >8 mmol/L, p = 0.275, over time (years) and per group (CSII vs. MDI). P-value is obtained from the linear mixed model.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

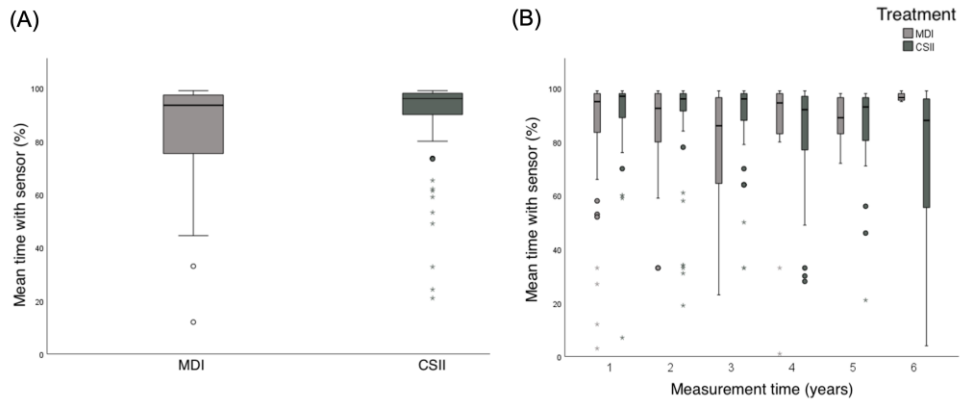

Figure 9. Mean time with sensor over time and per group (CSII vs. MDI).
(A) Mean time with sensor; and (B) boxplot of mean time with sensor, p = 0.246, over time (years) and per group (CSII vs. MDI). P-value is obtained from the Mann-Whitney U test.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Paper II

Among the 252 study participants, 80 (31.7%) had developed diabetic retinopathy and 172 (68.3%) had not 8–10 years after diagnosis of diabetes. Statistically significant findings in participants with retinopathy were: higher mean HbA1c (70.4±15.2 vs. 60.7±13.8 mmol/mol; p<0.0001), mean BMI (24.7(23.1–27.0) vs. 24.0(21.6–26.5) kg/m^2; p = 0.03), systolic blood pressure (124±10.5 vs. 120±11.9 mmHg; p = 0.02) and diastolic blood pressure (76.9±8.21 vs. 74.0±8.03 mmHg; p = 0.009) compared to participants without retinopathy. Significant differences in age at diagnosis of diabetes as well as in sex, were noted, where participants with development of retinopathy were younger at diagnosis (23.5±5.39 vs. 25.2±5.52 years; p = 0.03) and the proportion of men was higher (65.0 vs. 50.6%; p = 0.03). No significant differences were found between the groups (retinopathy vs. no retinopathy) regarding the type of diabetes (p = 0.64), the levels of ICA (p = 0.40) or tobacco use (p = 0.54). Furthermore, no significant differences were found between the groups (retinopathy vs. no retinopathy) regarding the levels of the adhesion molecules sE-selectin (p = 0.25), sICAM-1 (p = 0.93) or sVCAM-1 (p = 0.09).

Significant negative correlations were found between sICAM-1 and ICA (r_s = -0.19; p = 0.002), and sVCAM-1 and ICA (r_s = -0.13; p = 0.04) in participants with type 1 diabetes, whereas no correlation was found between sE-selectin and ICA.

Furthermore, no correlation was found between the levels of ICA and the age at diagnosis of diabetes.

In a logistic regression model with retinopathy as the dependent variable and mean HbA1c, mean BMI, systolic blood pressure, diastolic blood pressure, sex, and age at diabetes diagnosis as independent variables, all lost statistical significance except mean HbA1c (odds ratio 1.04 [95% CI: (1.02–1.07)]; p = 0.0001).

Participants with type 1 diabetes who had developed retinopathy 8–10 years after diagnosis of diabetes had statistically significantly higher mean HbA1c ($p<0.001$), mean BMI ($p = 0.019$), systolic blood pressure ($p = 0.002$) and diastolic blood pressure ($p = 0.003$), whereas the age at diagnosis of diabetes ($p = 0.015$) was lower compared to participants without retinopathy. The proportion of men was higher among those with type 1 diabetes and retinopathy, as compared to participants without retinopathy ($p = 0.026$). Regarding sE-selectin, sICAM-1, and sVCAM-1 in participants with type 1 diabetes no differences were observed between the groups with or without retinopathy.

In the type 2 diabetes group, no statistically significant differences regarding clinical data and mean HbA1c were found between those with development of retinopathy and without. Mean HbA1c was higher in the group with retinopathy although not reaching statistical significance ($p = 0.08$). However, sE-selectin, but not sICAM-1 or sVCAM-1, was significantly higher in the group with type 2 diabetes and retinopathy, as compared to the group without retinopathy (11.8(9.97–12.6) vs. 9.43(5.85–12.7) ng/ml; $p = 0.04$). Figure 10 shows an ELISA microplate.

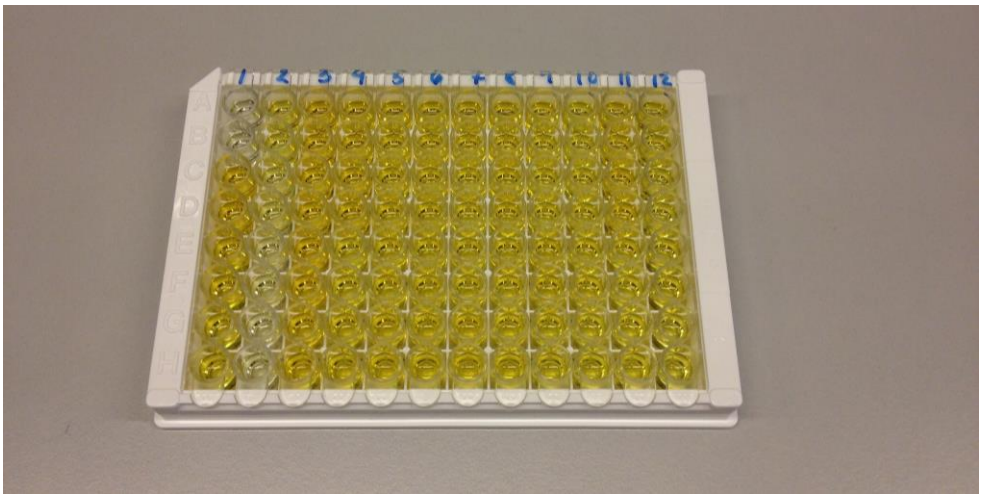

Figure 10. Photograph from the Diabetes Research Laboratory, BMC, Lund, showing an ELISA microplate directly after absorbance measurement in a FLUOstar Optima Microplate Reader. The photograph was taken by the author at the time when the author also conducted the laboratory analyses.

Figure 11 and Figure 12 illustrate the levels of the adhesion molecules in type 1 and type 2 diabetes with and without retinopathy.

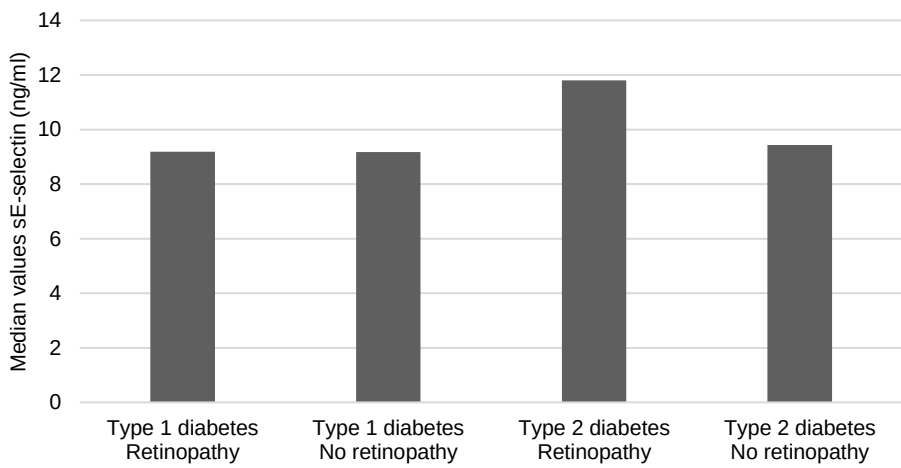

Figure 11. sE-selectin in type 1 and type 2 diabetes with and without diabetic retinopathy. In type 2 diabetes the median level of sE-selectin is significantly higher in the group with diabetic retinopathy compared to the group without, $p = 0.04$.

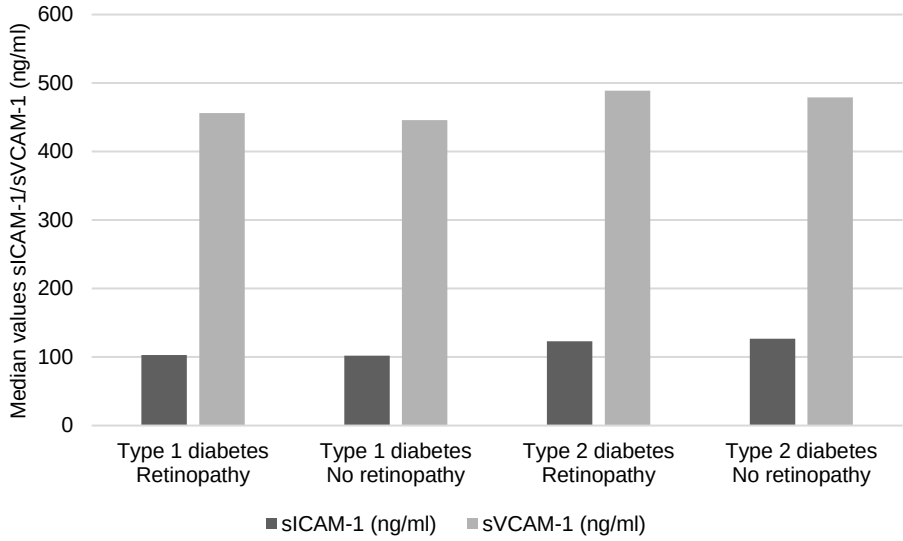

Figure 12. sICAM-1 and sVCAM-1 in type 1 and type 2 diabetes with and without diabetic retinopathy. No significant differences.

Table 7 presents clinical and biochemical data in further detail for study participants with type 1 and type 2 diabetes with and without development of retinopathy.

Table 7. Clinical and biochemical data for participants with type 1 and type 2 diabetes, aged 15 to 34 years at diagnosis of diabetes, with and without development of diabetic retinopathy 8 to 10 years after diagnosis of diabetes.

	Type 1 diabetes (n = 169)			Type 2 diabetes (n = 83)		
	Retinopathy (n = 52)	No retinopathy (n = 117)	P-value	Retinopathy (n = 28)	No retinopathy (n = 55)	P-value
At diagnosis of diabetes						
Male/female	35/17	57/60	p = 0.026	17/11	30/25	p = 0.59
Age (years)	22.9±5.27	25.1±5.53	p = 0.015	24.8±5.48	25.4±5.53	p = 0.65
ICA (JDF units)	512 (96-2000)	1000 (112-2000)	p = 0.43			
sE-selectin (ng/ml)	9.19 (6.53-12.5)	9.18 (7.11-12.1)	p = 0.83	11.8 (9.97-12.6)	9.43 (5.85-12.7)	p = 0.04
sICAM-1 (ng/ml)	103 (73.4-147)	102 (66.7-135)	p = 0.90	123 (94.8-178)	127 (84.4-185)	p = 0.96
sVCAM-1 (ng/ml)	456 (370-578)	446 (355-528)	p = 0.32	489 (420-617)	479 (371-574)	p = 0.24
At follow-up						
Mean BMI (kg/m^2)	24.1 (22.7-26.8)	23.3 (21.3-25.6)	p = 0.019	25.8 (23.7-27.2)	24.9 (22.9-28.6)	p = 0.84
Systolic blood pressure (mmHg)	126±9.55	120±11.8	p = 0.002	120±11.2	120±12.4	p = 0.89
Diastolic blood pressure (mmHg)	77.7±8.18	73.6±7.92	p = 0.003	75.4±8.19	74.7±8.30	p = 0.72
Tobacco use (yes/no)	23/27 (46%)	50/61 (45%)	p = 0.91	16/12 (57.1%)	26/29 (47.3%)	p = 0.40
Mean HbA1c IFCC (mmol/mol)	71.6±14.2	60.4±12.5	p<0.001	68.3±17.0	61.2±16.2	p = 0.08

The data are presented as mean ± SD, median (interquartile range) or number (proportion).
ICA, islet cell antibodies; JDF, Juvenile Diabetes Foundation; IFCC, International Federation of Clinical Chemistry.

Mean BMI was significantly lower in participants with type 1 diabetes compared with participants with type 2 diabetes ($p<0.001$), although no other differences in clinical data were found when comparing the two groups. sICAM-1 was statistically higher in the group with type 2 diabetes ($p = 0.001$), whereas no statistically significant differences were found between type 1 and type 2 diabetes regarding sVCAM-1 ($p = 0.07$) and sE-selectin ($p = 0.32$). Clinical and biochemical data for study participants with type 1 and type 2 diabetes are presented in Table 8.

Table 8. Comparison of clinical and biochemical data for participants with type 1 and type 2 diabetes at diagnosis of diabetes and at follow-up 8 to 10 years after diagnosis of diabetes.

	Type 1 diabetes (n = 169)	Type 2 diabetes (n = 83)	P-value
At diagnosis of diabetes			
Male/female	92/77	47/36	p = 0.74
Age (years)	24.4±5.54	25.2±5.48	p = 0.31
sE-selectin (ng/ml)	9.18 (7.04-12.2)	10.2 (7.00-12.6)	p = 0.32
sICAM-1 (ng/ml)	103 (67.2-138)	127 (88.5-181)	p = 0.001
sVCAM-1 (ng/ml)	450 (356-544)	479 (405-587)	p = 0.07
At follow-up			
Mean BMI (kg/m2)	23.7 (22.0-26.0)	25.1 (23.2-27.7)	p<0.001
Systolic blood pressure (mmHg)	122±11.4	121±11.9	p = 0.31
Diastolic blood pressure (mmHg)	74.9±8.20	74.9±8.22	p = 0.98
Tobacco use (yes/no)	73/88 (45.3%)	42/41 (50.6%)	p = 0.44
Mean HbA1c IFCC (mmol/mol)	64.1±14.0	63.7±16.7	p = 0.87

The data are presented as mean ± SD, median (interquartile range) or number (proportion).
IFCC, International Federation of Clinical Chemistry.

Paper III

Of the 72 participants with type 1 diabetes included in the study, 35 (48.6%) had developed diabetic retinopathy during the follow-up period of 15 to 23 years. All participants were followed for a minimum of 15 years after which 25 participants (34.7%) had developed retinopathy, as visualized in Figure 13 and Figure 14.

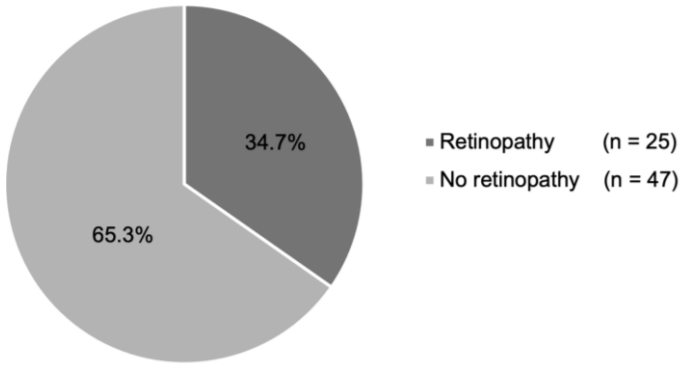

Figure 13. The proportion of participants with and without diabetic retinopathy 15 years after diagnosis of type 1 diabetes.

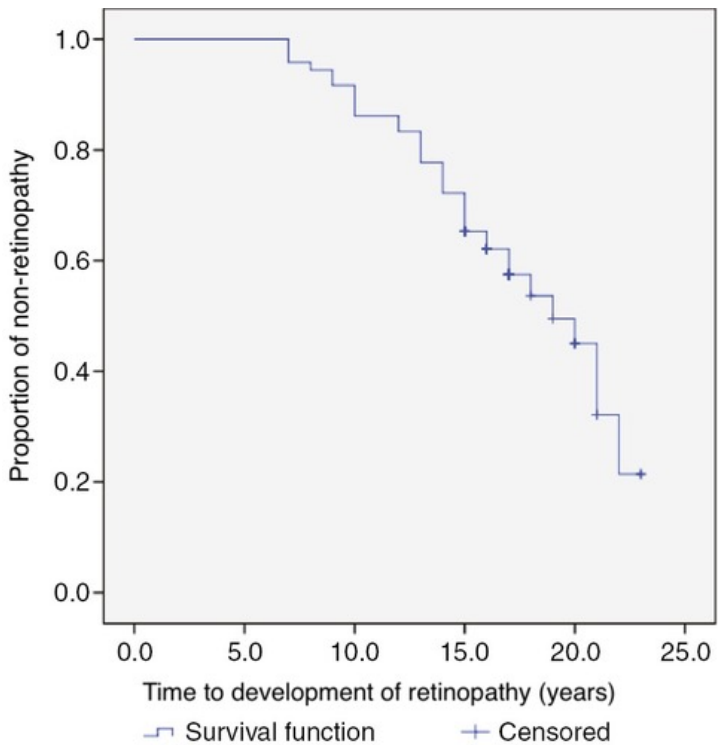

Figure 14. The Kaplan-Meier survival curve illustrating time from diagnosis of type 1 diabetes until development of diabetic retinopathy.

When comparing the variables recorded at the diagnosis of diabetes between those who had developed retinopathy after 15 years (n = 25) and those who had not (n = 47), no significant differences were observed in terms of sex, weight loss prior to diagnosis, weight at admission to hospital, weight at discharge from hospital, blood pressure, vP-glucose, C-peptide, vB-pH, base excess, ketoacidosis at diagnosis, family history of diabetes, ethnicity, and parental separation. However, HbA1c was significantly higher in those who had developed retinopathy after 15 years (98±9.2 (n = 25) vs. 86±9.2 (n = 46) mmol/mol; p = 0.025) compared to those who had not (Table 9). Furthermore, HbA1c at diagnosis of diabetes was significantly higher in females compared to males (10.2±2.0 (n = 34) vs. 9.1±1.7 (n = 37) %; p = 0.017). No significant differences were found between males and females regarding age, vP-glucose, vB-pH, and base excess at diagnosis of diabetes.

Table 9. Comparison of characteristics at the diagnosis of type 1 diabetes between those who had developed diabetic retinopathy 15 years after diagnosis and those who had not.

Characteristics	Retinopathy (n = 25)	No retinopathy (n = 47)	P-value
Male/female	14/11	23/24	0.747
Family history of diabetes (%)	15 (60.0) n = 25	27 (57.4) n = 47	0.967
Nordics (%)	25 (100.0) n = 25	45 (95.7) n = 47	0.540
Parental separation (%)	7 (29.2) n = 24	8 (17.4) n = 46	0.405
Age at diabetes diagnosis (years)	10.5 (3.7-17.0) n = 35	7.3 (1.0-16.0) n = 46	0.027
Weight loss (%)	16 (76.2) n = 21	17 (58.7) n = 29	0.321
Weight at admission (kg)	30.0 (14.5-81.0) n = 25	24.8 (10.3-65.6) n = 46	0.144
Weight at discharge (kg)	29.5 (16.0-59.5) n = 10	25.2 (11.3-72.2) n = 10	0.706
Systolic blood pressure (mmHg)	106.6±5.5 n = 9	110.9±15.4 n = 17	0.427
Diastolic blood pressure (mmHg)	65.3±10.6 n = 9	67.9±7.1 n = 16	0.521
vP-glucose (mmol/L)	23.1 (8.0-49.3) n = 25	25.7 (12.5-55.9) n = 47	0.619
HbA1c IFCC (mmol/mol)	98±9.2 (n = 25)	86±9.2 (n = 46)	0.025
C-peptide (nmol/L)	0.2 (0.1-0.7) n = 6	0.3 (0.1-0.4) n = 14	0.343
vB-pH	7.4 (7.2-7.5) n = 19	7.4 (7.1-7,5) n = 33	0.661
Base excess (mmol/L)	-2.0 (-19.0-2.0) n = 25	-2.0 (-30.0-4.0) n = 47	0.368
Ketoacidosis (%)	6 (24.0) n = 25	17 (36.2) n = 47	0.430

The data are presented as mean ± SD, median (minimum and maximum values) or number (proportion). IFCC, International Federation of Clinical Chemistry.

A negative correlation was identified between the age at diagnosis of diabetes and the time to development of retinopathy (r_s = -0.376; p = 0.026). No correlation was observed between the time to development of retinopathy and sex, vP-glucose at diagnosis and HbA1c at diagnosis.

Moreover, a negative correlation was identified between HbA1c values recorded 6 to 10 years after diabetes diagnosis and time to development of retinopathy

(r_s = -0.354; p = 0.037), as shown in Figure 15. No such correlation was observed for HbA1c values before or after this time span. When comparing the mean HbA1c per year over the first 15 years after diabetes diagnosis, those who had developed retinopathy had significantly higher mean HbA1c at years 2, 3, 5, 6, 7, and 8 compared to those who had not developed retinopathy.

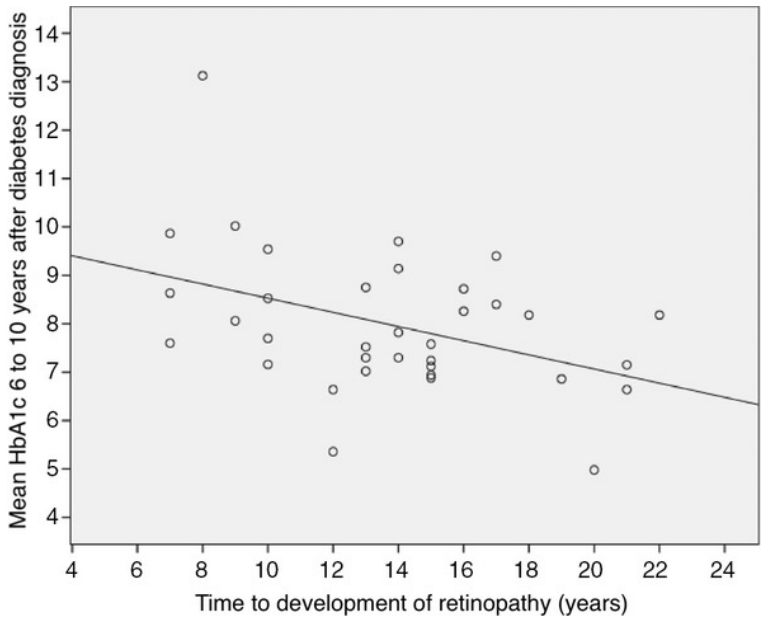

Figure 15. Spearman's rank correlation between mean HbA1c 6 to 10 years after diabetes diagnosis and time to development of diabetic retinopathy (r_s = -0.354; p = 0.037).

Paper IV

In the district where the study was conducted, the incidence of childhood type 1 diabetes has increased significantly ($p<0.001$) from the 1970s through 2013, which was assessed in a log-linear Poisson regression model illustrated in Figure 16.

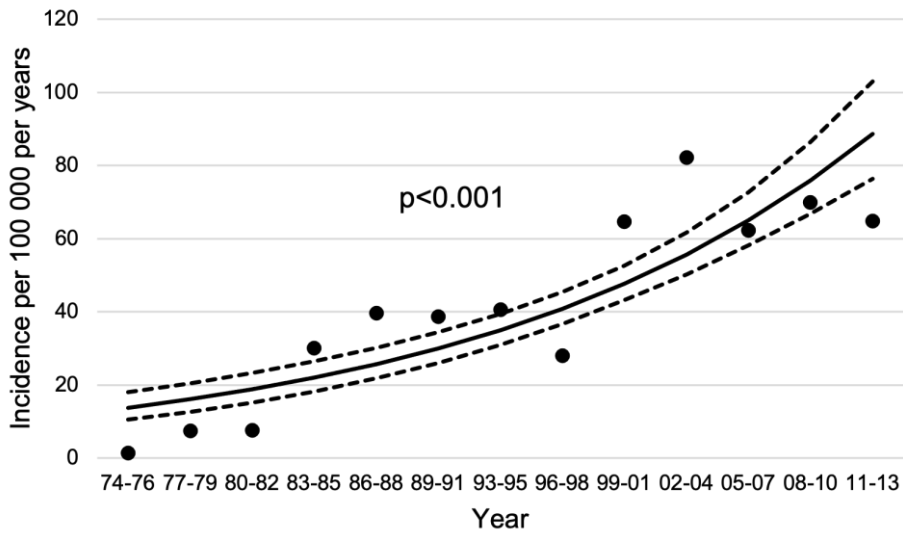

Figure 16. Incidence rate of childhood type 1 diabetes by years 1974 to 2013.
Observed (points) and trend (line) rates with 95% confidence interval (dashed line) predicted by a Poisson regression model.

This study conducted a comparative analysis of two cohorts of type 1 diabetes patients diagnosed during two different periods: 1993 to 1998, with a calculated incidence rate of 35 children and adolescents per 100,000 per year, and 2011 to 2013, with a calculated incidence rate of 65 children and adolescents per 100,000 per year. In the group diagnosed between 1993 and 1998, all participants were of Nordic origin, whereas in the 2011 to 2013 group, only 88.2% were of Nordic origin ($p = 0.01$). The remaining participants were immigrants from Serbia, Palestine, Iraq, Iran, Pakistan, and Saudi Arabia, with one child from each country. Three out of six immigrant children presented with ketoacidosis at diagnosis in 2011 to 2013. A significant difference was observed between the groups regarding the initial use of intensive care ($p = 0.03$), which was more prevalent in the 2011 to 2013 onset group. Furthermore, the prevalence of celiac disease was higher in the group diagnosed in 2011 to 2013, but this difference did not reach statistical significance ($p = 0.06$). No

significant differences were identified between the groups regarding sex, family history of diabetes, age at diabetes diagnosis, duration of symptoms, weight loss prior to diagnosis, weight and height at admission to hospital, BMI, weight at discharge from hospital, blood pressure, vP-glucose, HbA1c, C-peptide, vB-pH, base excess, ketoacidosis at diagnosis, associated diseases like hypothyroidism and celiac disease, parental separation or patients' use of alcohol and smoking. The results are presented in Table 10 and Figure 17.

Table 10. Comparison of characteristics at the diagnosis of type 1 diabetes between two groups diagnosed in 1993 to 1998 and 2011 to 2013.

Characteristics	Diabetes diagnosis 1993 to 1998 (n = 45)*	Diabetes diagnosis 2011 to 2013 (n = 51)**	P-value
Male/female	29/16	31/20	0.87
Family history of diabetes (%)	26 (61.9) n = 42	29 (56.9)	0.78
Nordics (%)	45 (100)	45 (88.2)	0.01
Age at diabetes diagnosis (years)	10.2 (5.9-14.5)	9.1 (6.2-12.7)	0.44
Duration of symptoms (days)	14.0 (7.0-21.0) n = 44	11.5 (3.5-21.0) n = 48	0.15
Weight loss (%)	25 (75.8) n = 33	30 (62.5) n = 48	0.10
Weight at admission (kg)	31.2 (20.5-46.3) n = 44	31.4 (20.8-39.2)	0.49
Height at admission (m)	1.5 (1.3-1.7) n = 32	1.3 (1.2-1.5) n = 46	0.08
BMI (kg/m^2)	16.4 (14.8-18.3) n = 32	16.4 (14.5-18.4) n = 46	0.56
Weight at discharge (kg)	32.9 (19.1-46.3) n = 24	33.5 (21.6-43.2) n = 40	0.92
Systolic blood pressure (mmHg)	110.8±14.8 n = 19	111.1±13.5 n = 39	0.93
Diastolic blood pressure (mmHg)	68.9±9.0 n = 18	68.8±12.0 n = 39	0.97
vP-glucose (mmol/L)	24.6±7.9 n = 40	25.3±11.2 n = 37	0.74
HbA1c IFCC (mmol/mol)	90±20.5 n = 44	83±27.4	0.15
HbA1c NGSP (%)	10.4±4.0 n = 44	9.7±4.7	
C-peptide (nmol/L)	0.25 (0.17-0.31) n = 31	0.23 (0.15-0.46)	0.98
vB-pH	7.38 (7.32-7.41) n = 18	7.36 (7.34-7.37)	0.06
Base excess (mmol/L)	-1.0 (-6.7-0.7) n = 43	-1.0 (-11.0-1.0)	0.68
Ketoacidosis (%)	14 (31.1)	16 (31.4)	0.98
Intensive care (%)	1 (2.2)	8 (15.7)	0.03
Hypothyroidism (%)	1 (2.3) n = 44	0 (0)	0.46
Celiac disease (%)	0 (0) n = 43	5 (10) n = 50	0.06
Parental separation (%)	13 (29.5) n = 44	7 (13.7)	0.10
Alcohol (%)	0 (0) n = 37	2 (3.9)	0.51
Smoking (%)	0 (0) n = 42	1 (2)	1.00

* n = 45 unless otherwise noted.

** n = 51 unless otherwise noted.

The data are presented as mean ± SD, median (interquartile range) or number (proportion).

IFCC, International Federation of Clinical Chemistry; NGSP, National Glycohemoglobin Standardization Program.

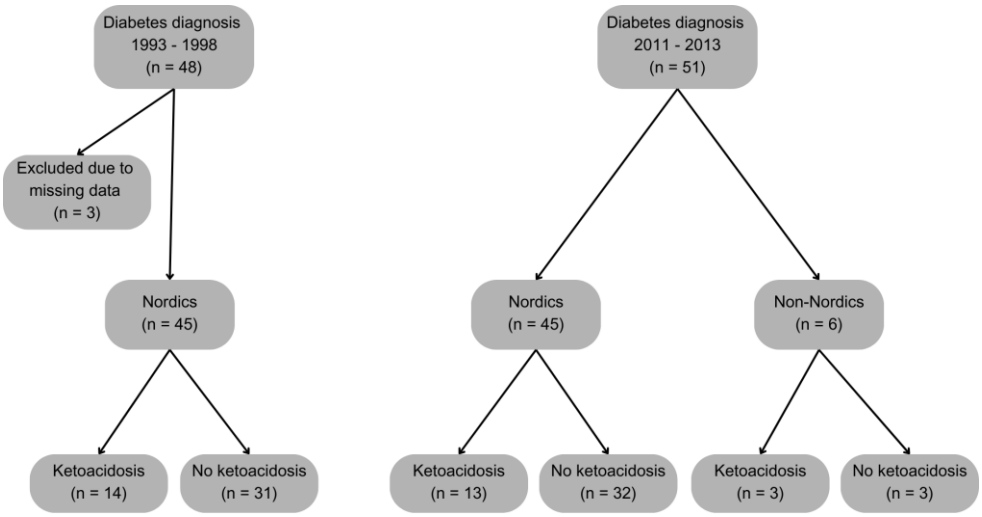

Figure 17. The two cohorts of study participants with type 1 diabetes, ethnicity and ketoacidosis at diagnosis.

Discussion

Type 1 diabetes is the most common form of diabetes in children and adolescents [172]. Managing type 1 diabetes is challenging for the youth and the whole family, and lifelong insulin therapy is required for survival. To achieve good outcomes, much is needed – insulin treatment via multiple daily injections or via an insulin pump, glucose monitoring, diabetes education, and guidance from experienced healthcare professionals. Poor glycemic control may result in the acute complications of hypoglycemia or ketoacidosis, as well as in chronic microvascular and macrovascular complications eventually [96]. A common denominator in the present work has been different perspectives on tailormade treatment for each patient for prevention of complications and for optimal quality of life.

All patients with diabetes have their unique needs that must be met. One patient might be physically highly active, whereas another one has a sedentary lifestyle. One patient has a very regular lifestyle, whereas another one has the opposite of that and might be travelling the world. One patient has a desire for multiple daily injection treatment, whereas another one wants the most advanced insulin pump and CGM. Between the extremes, anything is possible. A patient's needs might also change over time, which is especially evident for a child with type 1 diabetes when he/she goes through puberty. The diabetes team must be sensitive to all these factors and be inventive. There is a need for a varied set of diabetes equipment, the landscape of which is rapidly evolving, with significant advancements in CGM and AID systems. Studies of how diabetes technology works in real-life takes time, and due to the rapid development of new technologies, the results might be obsolete when they are ready.

The study in **paper 1** has been conducted in a population of children with type 1 diabetes during a time frame when transition to the latest available types of insulin pumps has taken place, as well as addition of universal use of CGM. Only a few participants used AID systems since such pumps only became available toward the end of the follow-up period. When comparing CSII and MDI, similar glycemic control was achieved in both groups, when CGM was used. This is consistent with previously published data concluding that glycemic control was affected more by using CGM than by the mode of insulin delivery with CSII or MDI [173-175]. A potential limitation of this study is that the participants have not been randomized to either CSII or MDI. Additionally, different pump types with varying levels of advanced functionality have been used, and some participants initially started on

sensor augmented pumps before transitioning to more advanced models. Nevertheless, without risk of extra personal financial burden thanks to the reimbursement system, each participant and parent/caregiver in the study could choose not only between CSII and MDI, but also among different pump types on the Swedish market. Another strength of the study is the length of the follow-up period, which in comparison with other studies in this field could be considered long [153, 176].

Modern CSII, particularly with AID functionality, provides support in achieving good glycemic control, while also enhancing quality of life and reducing the burden of diabetes management for children with type 1 diabetes and their families [160, 177-181]. When the patient and/or caregiver has freedom of choice between CSII and MDI, considering what best suits the individual, good glycemic control can be obtained either by CSII or MDI, when CGM is being used. Having the freedom to choose between treatment options is an important aspect of maintaining a good quality of life.

Looking ahead, clinicians working in diabetes care will need in-depth knowledge of available diabetes technology systems to guide the youth and their parents/caregivers in selecting the most appropriate treatment. Establishment of high-quality, efficient, and easily accessible educational resources is essential for diabetes teams as well as for the youth and their families. Focusing on the unique needs of each patient with diabetes, as well as their individual ability to use the devices safely and effectively, is key.

Unsuccessful management of diabetes will lead to the development of severe complications later in life [105, 114]. About a third of people with diabetes have signs of diabetic retinopathy, and even more for people with type 1 diabetes [106, 112]. There is a concern for the increasing prevalence of type 2 diabetes and retinopathy. As previously shown, younger patients with type 2 diabetes have a higher prevalence of severe retinopathy than younger patients with type 1 diabetes [115]. Thus, prediction of retinopathy at an early stage, and thereby recognizing high-risk patients for development of retinopathy, would be desirable. Healthcare could then be individualized, with resources and screening programs being focused on patients with the most urgent needs. Potentially, in the future, the onset of retinopathy can be delayed or prevented, providing benefits not only for the individual but also for society and the payers.

Due to the role of soluble adhesion molecules in endothelial activation, their increased levels could potentially indicate the risk and severity of retinopathy development [123, 124, 127, 128]. The study in **paper II**, showed that sE-selectin may serve as a predictive biomarker for the development of retinopathy in type 2 diabetes, similar to the results in the DCCT/EDIC studies regarding type 1 diabetes [135]. Previously, increased levels of sE-selectin have been shown to be associated with insulin resistance and hyperinsulinemia [182], which may support the results

in **paper II** that show significantly increased levels of sE-selectin, but not sICAM-1 or sVCAM-1, in the group with retinopathy and type 2 diabetes. In participants with type 1 diabetes, no differences were observed between the groups with or without retinopathy regarding sE-selectin, sICAM-1, or sVCAM-1.

The study in **paper II** confirmed that suboptimal glycemic control measured as mean HbA1c, over the course of the disease, is a strong predictor for development of retinopathy in type 1 diabetes. Besides that, our results showed that the clinical characteristics suboptimal glycemic control during follow-up, higher mean BMI, higher systolic and diastolic blood pressure, male sex, and younger age at diabetes diagnosis, were associated with development of retinopathy in type 1 diabetes, but not in type 2 diabetes. However, only mean HbA1c remained as a risk factor in a multivariate analysis.

This prospective study is part of the nationwide study, K-DISS, which includes a well-defined cohort of young adults with type 1 or type 2 diabetes and features a long follow-up period of 8 to 10 years. The study design allowed for longitudinal identification of microvascular complications. To ensure the accuracy of the findings, patients who developed nephropathy or the combination of nephropathy and retinopathy during follow-up were excluded not to risk investigation of patients with nephropathy caused by conditions unrelated to diabetes.

In this study, only baseline levels of the adhesion molecules were analyzed, limiting the results to a single measurement. Although the adhesion molecules measured have been shown to remain stable in stored specimens, some degradation may have occurred due to long storage time. The majority of those who develop type 2 diabetes are diagnosed later in life, whereas this study focused on adolescents and young adults. A broader age range could therefore have impacted the results. The time interval between onset and diagnosis of type 1 and type 2 diabetes may differ with type 2 diabetes often having a longer asymptomatic period before diagnosis. Therefore, there was a risk of microvascular complications already at diagnosis and time of inclusion in the study for the participants with type 2 diabetes. The number of participants with onset of type 2 diabetes in adolescence and early adulthood was small, but since the number of patients with type 2 diabetes is increasing globally with diagnosis being made at younger and younger ages, the results might be of interest [61].

HbA1c, which is a well-known predictive biomarker for the development of diabetic retinopathy [109-111, 183], is further studied in **paper III**. Despite reasonable glycemic control, patients with diabetes may develop microvascular complications, indicating the existence of also other risk factors. When comparing characteristics, recorded at the diagnosis of type 1 diabetes, between children and adolescents who developed retinopathy 15 years after diabetes diagnosis and those who did not, HbA1c was the strongest predictor of retinopathy. In this study, HbA1c was higher in females compared to males at diabetes diagnosis. There is, however, no clear

difference in the development of retinopathy between males and females. In the K-DISS cohort of adolescents and young adults in **paper II**, male sex was associated with development of retinopathy in type 1 diabetes. Independent of other risk factors, male sex was significantly associated with progression of retinopathy in type 1 diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII [111]. However, in an Australian study, a higher prevalence of retinopathy in type 1 diabetes has been reported for adolescent girls compared to boys [184]. The difference between sex and the development of retinopathy described in previous research might depend on the age of onset of diabetes or hormonal differences during puberty. In the study in **paper III**, a negative correlation was identified between the age at diagnosis of diabetes and the time to development of retinopathy. In the K-DISS cohort, aged 15 to 34 years at diagnosis, in **paper II**, younger age at diagnosis of type 1 diabetes was associated with development of retinopathy. These findings from **paper II** and **paper III** are consistent with a study reporting higher risk of vascular complications in those living with diabetes during puberty, compared to young people developing diabetes after puberty [185]. Screening for early signs of retinopathy, thereby identifying risk factors that can be addressed during adolescence, is of importance.

Effective and individualized diabetes treatment, aiming at the best possible glycemic control and optimal quality of life, is of utmost importance since, in recent decades, the incidence of childhood type 1 diabetes has increased in Sweden as well as globally [6, 11]. While the etiology of type 1 diabetes remains unknown, a combination of genetic and environmental factors is believed to play a role. The study in **paper IV** investigated demographic and disease related factors associated with the onset of type 1 diabetes during childhood in two distinct periods characterized by lower and higher incidence, respectively. The study could not provide clear explanations for the causes or the respective contributions of genetic and environmental factors to the increase in incidence. In fact, the incidence increased despite immigration from areas with lower risk of diabetes. Even though the genetic landscape of the population has evolved, there has been a significant increase in the incidence rate in the district since the 1970s, suggesting the influence of environmental factors. This aligns with findings from the United Kingdom [40]. On the contrary, a Swedish study examining parental country of birth, indicates that geographical variations in childhood type 1 diabetes may be more influenced by genetic susceptibility than by environmental factors [186]. It is possible that various environmental factors, like dietary habits, may be transferred from one region to another [186]. Although the number of non-Nordics was significantly higher in the group with higher incidence of type 1 diabetes, this difference in ethnicity did not impact the characteristics at the diagnosis of type 1 diabetes or the overall incidence of the disease. Notably, the significant difference in the initial use of intensive care should be interpreted with caution due to a limited sample size and potential changes in the indications for intensive care over time. The proportion of cases presenting with ketoacidosis was consistent between both groups, with 31.1% and 31.4%,

respectively. This is in line with findings from a study from the United States indicating a stable ketoacidosis prevalence over time with almost one-third presenting with ketoacidosis, although higher among minority populations [91]. In 2011 to 2013, three out of six children with immigrant parents presented with ketoacidosis in this study. It is reasonable to assume that the prevalence of ketoacidosis would be lower in the 2011 to 2013 group, due to improved knowledge and awareness of type 1 diabetes in recent years in the population.

The studies in **paper III** and **paper IV** focused on examining the trends among children and adolescents with type 1 diabetes over time within a specific geographical area in southern Sweden. A notable strength of the studies lies in their inclusion of all available cases during the studied periods. Despite this strength, the studies were constrained by small sample sizes, presenting a limitation and potential underpowering. These limitations may have contributed to the observed outcomes, where only few significant differences were identified. Moreover, it would have been beneficial to explore potential genetic variations and differences in diabetes related autoantibodies between the groups, which unfortunately was not possible due to the absence of genetic and autoantibody data in the group diagnosed in the 1990s. While residential areas and life events were examined, the limited numbers precluded meaningful interpretation.

Conclusions

The conclusions drawn from the results of this work are summarized below.

I. No differences in glycemic control were found between treatment with insulin pump and insulin pen in a real-world pediatric type 1 diabetes setting with freedom of choice between these two modes of insulin delivery, without impact on financial burden on the patient level, and with universal use of CGM. CGM might be a stronger differentiator for glycemic control than the mode of insulin delivery.

II. Soluble E-selectin might be considered a potential predictor for development of diabetic retinopathy in type 2 diabetes. For soluble ICAM-1 and soluble VCAM-1, no such predictive roles could be identified neither for type 1 diabetes nor for type 2 diabetes. HbA1c and clinical characteristics predicted development of diabetic retinopathy in type 1 diabetes.

    In type 1 diabetes, significant negative correlations were found between soluble ICAM-1 and ICA, and between soluble VCAM-1 and ICA. It is yet to be determined whether the soluble adhesion molecules are independent of ICA status or not.

III. In childhood type 1 diabetes, higher HbA1c was associated with shortened time to development of diabetic retinopathy. Hence, keeping HbA1c as close to normal as possible is essential.

    A significant negative correlation was identified between the age at diagnosis of type 1 diabetes and the time to development of diabetic retinopathy.

IV. In the district in southern Sweden where the study was conducted, the incidence of childhood type 1 diabetes has increased, despite immigration from areas with lower risk of diabetes.

Future perspectives

Since AID systems became available toward the end of the study, few participants used such systems. Therefore, an interesting avenue for future research would be to longitudinally compare AID systems to MDI/traditional insulin pumps when CGM is used. Furthermore, as this study did not evaluate the aspect of quality of life, future studies are encouraged to include this dimension.

For future research, studies with larger sample sizes, broader age ranges and longer follow-up periods would be valuable for the uncovering of new biomarkers for prediction of diabetic retinopathy. The broader age range could provide a better understanding of biomarkers for diabetic retinopathy particularly in type 2 diabetes since those who are diagnosed with type 2 diabetes often are older. Additionally, as this study only measured levels of biomarkers at the diagnosis of diabetes, it would be interesting to measure levels of biomarkers throughout the follow-up period as well.

Since the genetic predisposition affects time to development of diabetic retinopathy, it would be of value to study genetics further. To shed more light on genetic and environmental factors causing type 1 diabetes, future research should, in addition to including larger study populations, also examine genetic variations and diabetes related autoantibodies.

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Diabetes mellitus in young people

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