Differences in glycemic control in type 1 diabetes children and adolescents in a national and international perspective and the effect on microvascular complications in young adults

Johan Anderzén
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“Allt nytt vi får lära oss gör vår värld större, vi får ytterligare ett sammanhang att foga till de andra i vår evigt expanderande världsbild.”

Mark Levengood

To my family and colleagues
ABSTRACT

This thesis focuses on glycemic control measured as HbA1c in type 1 diabetes (T1D) patients during childhood and especially during adolescence, both in a Swedish and an international context, and relates the glycemic control to the risk of complications in young adults.

In studies I and II, the Swedish Pediatric Diabetes Quality Register (SWEDIABKIDS) and the Swedish National Diabetes Register (NDR) were used. More than 4000 young adults with T1D and data on HbA1c in NDR both in 2011 and 2012 as well as data on HbA1c in SWEDIABKIDS were used. The T1D patients with poor glycemic control during their teenage period had a risk for retinopathy several times higher than those with good glycemic control. The risk for micro- and macroalbuminuria was also higher in those with poor glycemic control and was most pronounced in the T1D patients with high HbA1c in both registers. Females had worse glycemic control than males during the teenage period and an increased risk of retinopathy as young adults.

In studies III and IV, pediatric diabetes quality register data from, respectively, eight and seven Western high-income countries were collected in the year 2013. Data on about 60 000 T1D patients were analyzed according to mean HbA1c levels in the countries and related to actual age and T1D duration to determine if there were differences in glycemic control between the countries. There were large differences in mean HbA1c between the countries, both when related to age and T1D duration. Despite the differences in mean HbA1c, the increase in mean HbA1c with increasing age and T1D duration was very similar in all countries.

The overall picture of these studies is that good glycemic control is very important to avoid complications of T1D as young adults, and it seems particularly important to maintain a good glycemic control during adolescence. Furthermore large differences in glycemic control in T1D patients in Western high-income countries were found. Despite the differences in glycemic control, the pattern of rising HbA1c with increasing age and duration of T1D was very similar in all countries. Females have worse glycemic control than males during their teenage period, both in Sweden and internationally, and they also have more retinopathy as young adults.

This thesis shows that it is of the utmost importance to treat T1D patients intensively directly after diagnosis, to treat the young T1D patients intensely and to reduce the rise in HbA1c with increasing age and duration of T1D in order to avoid complications early in life. Diabetes quality registers give the opportunity to compare results and share experiences, both within and between countries, so treatment of T1D can be designed in the best possible way and thereby minimize T1D complications.
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I. Teenagers with poor metabolic control already have a higher risk of microvascular complications as young adults
J. Anderzen, U. Samuelsson, S. Gudbjornsdottir, L. Hanberger and K. Akesson
J Diabetes Complications 2016 Vol. 30 Issue 3 Pages 533-6

II. Teenage girls with type 1 diabetes have poorer metabolic control than boys and face more complications in early adulthood
J Diabetes Complications 2016 Vol. 30 Issue 5 Pages 917-22

III. International benchmarking in type 1 diabetes: Large difference in childhood HbA1c between eight high-income countries but similar rise during adolescence. -A quality registry study
Pediatr Diabetes 2020 Vol. 21 Issue 4 Pages 621-627

IV. HbA1c during the first 3-6 months after diagnosis is associated with long term mean HbA1c in seven high-income countries. -A quality registry study

Submitted for publication
ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>CGM</td>
<td>Continuous glucose monitoring</td>
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<td>DanDiabKids</td>
<td>The Danish National Diabetes Register</td>
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<tr>
<td>DPV</td>
<td>The Prospective Diabetes Follow-up Register (Germany, Austria)</td>
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<td>DCCT</td>
<td>The Diabetes Control and Complications Trial Research Group</td>
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<td>LOESS</td>
<td>Locally weighted regression scatter plot smoothing</td>
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<td>NCDR</td>
<td>The Norwegian Childhood Diabetes Register</td>
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<td>NDR</td>
<td>The Swedish National Diabetes Register</td>
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<td>NHW</td>
<td>Non-Hispanic white race/ethnicity</td>
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<td>NPDA</td>
<td>The National Paediatric Diabetes Audit (England, Wales)</td>
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<td>SWEDIABKIDS</td>
<td>The Swedish Pediatric Diabetes Quality Register</td>
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<td>T1D</td>
<td>Type 1 diabetes</td>
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<td>T1DX</td>
<td>The T1D Exchange (USA)</td>
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<td>TIR</td>
<td>Time in range</td>
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<td>TIT</td>
<td>Time in target</td>
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PROLOGUE

When I, as a young resident in pediatrics, met children and adolescents with type 1 diabetes (T1D) many of them did not reach the target for HbA1c. Especially the adolescents seemed to have a hard time achieving good glycemic control. Asking senior colleagues for advice, two different ways to tackle the task emerged. Some argued that having good glycemic control during the teenage period is crucial for future health, while others claimed that when the teenagers grew older they would get wiser and improve their glycemic control. “A few years of poor glycemic control can’t be that bad; give them some slack”.

These two very different ways to handle the problem piqued my curiosity and soon I realized that much was unknown about how glycemic control during the adolescent period affects the risk of complications related to T1D. My journey toward this thesis had started, with the hypothesis that the teenage period is a very important period of life and that good glycemic control is crucial to gain better health and avoid complications.
BACKGROUND

A brief history of diabetes
A deadly disease with sweet tasting urine was already described in the ancient Greek, Egyptian and Chinese literature and named as diabetes in Greece around 250 BC (1). In 1869, in his doctoral thesis, Paul Langerhans described the structure in the pancreas which later was called the islets of Langerhans (2), and in 1890 Minkowski and von Mering published a paper where they stated that dogs with pancreas extirpation developed diabetes (3). The big breakthrough came in 1922 when Banting et al. gave diabetes patients an extract from the pancreas and showed that the patients had less glucose in the urine and that the acetone excretion in the urine disappeared (4). Since then, therapies have developed enormously with sensitive ways to follow the patient’s glucose level and new technical achievements that help with the administration and dosage of insulin. Although T1D is no longer a disease with a certain deadly outcome, it can still lead to medical complications and premature death (5-8). During the 80s and 90s the Diabetes Control and Complications Trial Research Group (DCCT) and others showed that intensive treatment with good glycemic control measured as HbA1c is very important for both achieving well-being and particularly for avoiding complications (9-13). Follow-up studies have shown a decreased long-term risk for micro-and macrovascular complications (14-17).

The incidence of T1D in children and adolescents vary around the world, with the highest incidence in high-income countries and especially in Finland and Sweden, while most deaths related to diabetes are seen in low- and lower-middle income countries (18).

The history of healthcare registries
The first medical register was started in Norway in 1856. The aim of the register was to try to better understand the rising numbers of leprosy in the country (19). In Sweden the Swedish Knee Arthroplasty Register was the first medical register to start in 1975 and a few years later the Swedish Hip Arthroplasty Register started. Both of them had the aim of improving and sharing knowledge of orthopedic arthroplasty surgery around the country (20). Since then, numerous healthcare registers have developed over the years all over the world. In 2021 Sweden had more than 100 national quality registers related to healthcare (21).

The German diabetes register (DPV) started in 1990 (22) as one of the first diabetes registers for children and adolescents, and as the years have gone by, also data from Austria, Switzerland and Luxemburg have been included in the register (23). The Swedish pediatric diabetes quality register (SWEDIABKIDS) was established in 2000 and since 2007 all pediatric clinics in Sweden have participated with a 98 % coverage rate of pediatric T1D patients (24). In Sweden, when T1D patients turn 18 years of age, data on them are recorded in the adult part of the Swedish National Diabetes Register (NDR). Data on patients’ HbA1c and complications can therefore be followed from diagnosis throughout life. The NDR was launched in 1996 and has
a coverage rate of 84.5% of adult patients with diabetes (24, 25). Since 2018 the Swedish pediatric diabetes quality register (SWEDIABKIDS) is an integrated part of the National Diabetes Register in Sweden that includes persons of all ages with T1D.

Both national and international diabetes registers, for children and adolescents, have made it possible to compare results but also to share knowledge and improve the outcome for children and adolescents with T1D. There is also a possibility to see trends in glycemic control and complications over time (26-29).

**Definition of diabetes**
At the time of our studies the definition of diabetes was (30):

Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL).

or

Fasting plasma glucose ≥ 7.0 mmol/L (≥126 mg/dL). Fasting is defined as no caloric intake for at least 8 h

or

2-h postload glucose ≥ 11.1 mmol/L (≥200 mg/dL) during an oral glucose tolerance test (OGTT).

Today an HbA1c ≥ 48 mmol/mol is an additional criterion for T1D diagnosis (31).

**Epidemiology**
Over 100 000 children under 15 years of age are diagnosed with T1D every year and currently about 600 000 children have T1D (32-34). T1D during childhood is more common in males than females 53% and 47% respectively (24, 35). There are large continental and regional differences in the incidence of T1D (Figure 1). The incidence of T1D for patients under 15 years of age in the USA and Europe except Scandinavia is 10-20 per 100 000 and in Scandinavia 30-60 per 100 000 (36, 37). The incidence in South America and Asia is as low as 1-3 per 100 000 (34).

The incidence rate of T1D in children in Europe has increased annually since 1989 (36) and is estimated to continue to do so in the future (38).
Pathogenesis
Type 1 diabetes is an autoimmune disease with destruction of β-cells in the pancreas and loss of insulin production (39). The autoimmune paths are complex and not fully understood. A recent study shows that bacterial translocation from the small bowel to the pancreas could be one of the factors involved in causing the damage to the β-cells of the pancreas (40). Several auto-antibodies are known to be involved in the process (41, 42).

Three phases of T1D are suggested. The autoimmune process from start to symptoms of T1D takes months to years. During the first phase the patient has no symptoms and is normoglycemic but autoimmune processes have started the destruction of β-cells. In phase two, there are still no symptoms, the destruction continues and the patient starts having a problem regulating the blood glycemic levels. In the third and last phase when 60 to 90 % of the β-cells are destroyed the symptoms of diabetes start and evolve (polyuria, polydipsia and polyphagia) (41, 42).

HbA1c
Glycated hemoglobin (HbA1c) was first isolated in the late 1950s (43) and characterized as a glycoprotein during the 1960s (44, 45). In the late 1960s, HbA1c was shown to be increased in diabetic patients (46). Elevated HbA1c in diabetes patients was shown in a systematic way in 1971 where a double increase in HbA1c was seen in T1D patients compared to controls but no relation was seen with complication rates or duration of T1D (47). The first large study to prove
that HbA1c could be used as marker of glycemic control was the DCCT study, where it was also shown that complication rates were related to glycemic control measured as HbA1c (9). At first the HbA1c results were not comparable between different laboratories so the National Glycohemoglobin Standardization Program (NGSP) (%) and later the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (mmol/mol) standardized the methods during the 1990s and 2000s (48) e.g. 7.4 % is equivalent to 57 mmol/mol and 9.3 % is equivalent to 78 mmol/mol.

Glucose enter the erythrocyte through GLUT-1 channels and binds to the β-chain of hemoglobin which is equivalent to the extracellular concentration of glucose and gives a proxy of the mean glucose levels during the last 120 days. Interestingly the organs that classically are affected by complications in diabetes also have GLUT-1 channels (49).

People with Asian, Black or Latino Ethnicity have slightly higher HbA1c than people with a Caucasian background. The reason for this is still unknown but biological and genetic factors have been proposed as potential factors. Serious inflammatory processes, hypothyroidism, hemoglobinopathies and other conditions that can affect the life time of the erythrocyte can have some effect on the HbA1c levels (49-52).

**Glycemic control over time**

Mean HbA1c during childhood (as a marker for glycemic control) improved in Sweden during the decade before our studies (53, 54). The mean HbA1c has continued to decrease since then and in 2021 the mean HbA1c for children in Sweden under 18 years of age was 53 mmol/mol (24) (Figure 2). Part of the explanation for the improvement could be the quality improvement collaborative (QIC) in Sweden. Differences in the various diabetes teams' approaches and results were highlighted and discussed in seminars and good examples were shared, which resulted in more equal care between the diabetes teams and improved glycemic control (28). The same trend of quality improvement projects and better glycemic control has also been seen in an international perspective (26, 55).

During the last few decades continuous glucose monitoring (CGM) technology has developed, and during recent years nearly 100 % of Swedish T1D patients under 18 years of age have used this technology (24, 56). The new technology has made it possible to measure in which proportions the glucose is between different levels, the so-called time in range (TIR) (3.9-10.0 mmol/l) and time in target (TIT) (4.0-8.0 mmol/l) (24, 56, 57). The correlation between HbA1c and TIR is moderate (58) but a higher TIR is correlated with a lower risk for microvascular complications (59). Time in target has a correlation with HbA1c; increased TIT correlates with lower HbA1c (60).
Figure 2. Mean HbA1c in T1D patients during childhood in Sweden 2004-2021

Diabetes complications over time

With insulin treatment, T1D was no longer a disease with an inevitable certain deadly outcome, but severe complications related to T1D were unavoidably with longer duration of disease (61). In the 1960s and 1970s, scientists noticed that better glucose control reduced the number of complications (62, 63). At the beginning of the 80s the first biosynthetic human insulin was developed and the insulin treatment was usually taken twice a day (64, 65). In 1993, DCCT published their results where they showed that intensive insulin treatment was outstanding compared to the former treatment regimens (9). Their result marked the start of more intense treatment of T1D. Thereafter the complications rates related to T1D have gradually decreased but it is still a challenge for healthcare providers to help patients to further improve HbA1c in order to continuously reduce complication rates (15).

Risk factors for mortality and complications

Although the treatment strategies have improved over time several studies have shown a significantly higher risk of premature death compared to a population without type 1 diabetes (5, 6, 66). T1D patients with low socioeconomic status have a higher risk for premature death and higher morbidity due to worse glycemic control (67). Other known factors for higher morbidity and mortality in T1D patients are smoking, high blood pressure, low physical activity, dysregulated cholesterol and overweight (68-70).

Smoking

Non-smokers have better glycemic control than smokers (71, 72). As a group, smokers have a more unhealthy lifestyle than non-smokers which may be part of the explanation (73) but there
are also studies where HbA1c, independently of other risk factors is higher in smokers (74, 75). The risk for vascular disease is increased in T1D patients, and in T1D patients who are smokers the risk for complications is even higher. The good news is that the increased risk due to smoking seems to decline if smoking stops (75).

Physical activity
Physical activity in people with T1D is desirable. In childhood, 60 minutes of exercise per day is recommended, which far from all achieve (76). Exercise in T1D patients improves the glycemic control, lowers the risk for retinopathy and microalbuminuria, but also lowers the risk for ketoacidosis (77, 78). The effects of physical activity on HbA1c and reduced complication risk are believed to derive from increased insulin sensitivity, improved lipid profile and beneficial effects on the endothelial function (79-81).

Overweight
People with T1D have a higher Body Mass Index (BMI) than people without T1D (82). It is a paradox that intensified insulin treatment is needed to maintain good glycemic control but at the same time intensified insulin treatment can increase weight gain and overweight leads to increased insulin resistance and makes it harder to maintain good glycemic control (82, 83).

Retinopathy
Blindness related to diabetes is one of the leading causes of loss of sight and is strongly related to poor glycemic control (9). Diabetes retinopathy arises from a complex pathophysiology due to hyperglycemic-induced metabolic stress which involves both vascular and neuronal damage (84). Hyperglycemia causes oxidative stress, inflammation and hypoperfusion in the retina. That leads to microaneurysms and local ischemia, non-proliferative diabetic retinopathy (NPDR), and in a later stage new blood vessels are formed, so-called neovascularization, which leads to a more permanent damage to the retina, proliferative diabetic retinopathy (PDR) (85). The early stage of NPDR is reversible if good glycemic control is achieved (86). Screening and treatment programs have improved the care and vision for patients with diabetes over time (87).

Nephropathy
Diabetes is worldwide the most common reason for kidney transplantation (88). Diabetes nephropathy is due to oxidative stress, glomerular hyperfiltration, hyperinflammation and fibrosis (89). The damage to the kidneys for patients with diabetes is specific and due to microvascular damage (90). Albuminuria is measured with urine albumin excretion test. Two out of three positive urine samples suggests a diagnosis of albuminuria (91). Diabetes nephropathy can be divided into microalbuminuria, macroalbuminuria and end-stage renal disease where only the last stage leads to clinical symptoms (92, 93). The DCCT study showed that intensive treatment reduced the kidney damage significantly nearly 20 years after the start of the study (14, 16). The microalbuminuria can be regressed but like retinopathy, it is an indication of damaged blood vessels.
Neuropathy

Neuropathy is a common complication of diabetes and about 50% of patients with diabetes will at some stage develop neuropathy (94). Usually the lower parts of the legs and the hands are affected symmetrically, with altered sensation (94). Glycemic control measured as HbA1c and duration of diabetes are the two main risk factors to develop diabetes neuropathy (95). The exact mechanism is still unknown but hyperglycemia and the changed insulin signaling together with altered blood flow in diabetes patients are known to be part of the explanation (96).

Cardiovascular complications

T1D patients have a several times higher risk for cardiovascular disease (CVD) than people without T1D (97, 98). The mechanism is not fully understood but oxidative stress due to hyperglycemia which leads to atherosclerosis seems to be part of the explanation (99). The risk has decreased during the last few decades, due to better glycemic control for T1D patients, but is still high (15, 97). Children diagnosed with T1D before the age of 10 are at higher risk of CVD than people diagnosed later in life, and females with early T1D diagnosis have a particularly high risk of CVD early in life (100).
HYPOTHESES AND AIMS

General aim

The main objective of this thesis is to gain additional understanding about glycemic control during the childhood period and specifically during the teenage period, in Sweden and internationally, and to discover how glycemic control during adolescence affects T1D complications in young adults.

Hypotheses

Good glycemic control during adolescence is important to prevent T1D complications in young adults.

Teenage females have poorer glycemic control and more T1D complications as young adults than males.

There are differences in glycemic control between high-income countries.

HbA1c during the first year after diagnosis predicts HbA1c level later.

Specific aims

Paper I To explore the relation between glycemic control during adolescence in individuals with T1D, with glycemic control and microvascular complications when the individuals have become young adults.

Paper II To compare glycemic control, measured as HbA1c, between males and females with type 1 diabetes during adolescence and as young adults and its effects on microvascular complications.

Paper III To identify differences and similarities in HbA1c levels and patterns regarding age and gender in eight high-income countries.

Paper IV To explore if HbA1c level at 3-6 months after diagnosis in seven high-income countries respectively could be part of the explanation for the different HbA1c levels with longer diabetes duration.
PATIENTS AND METHODS

The Swedish cohort

In studies I and II the National Diabetes Register for adults (NDR) and children (SWEDIBAKIDS) was used. Patients with HbA1c values registered in SWEDIBAKIDS between the age of 13 and 18 years that also had data on HbA1c in NDR in both 2011 and 2012 were included. In total, 4250 patients fulfilled the inclusion criteria. As seen in figure 3, 93.5 % were under the age of 31 years, which means that the study population consisted mainly of young adults.

Figure 3. Actual age in 2012. Percentage of the study population N=4250

The cohort was divided into groups depending on their glycemic control, < 57 mmol/mol, 57-78 mmol/mol and > 78 mmol/mol. At the time of the studies the HbA1c target in Sweden was 57 mmol/mol and > 78 mmol/mol was considered as poor glycemic control, where interventions were needed. The HbA1c groups were used to determine if the glycemic control during the teenage period and as young adults affects the risk of complications early in life but also to compare glycemic control between males and females and their risk for complications related to their HbA1c level.

Data on microvascular complications, (retinopathy, micro- and macroalbuminuria), in NDR both in 2011 and 2012 were used. Fundus photography was used to diagnose retinopathy, and even simplex retinopathy, if seen in two different examinations, was interpreted as retinopathy.
Retinopathy both in 2011 and 2012 was acquired to be included in the retinopathy group in the studies.

Albuminuria was measured with a urine albumin excretion test, where diagnosis was defined as two out of three consecutive positive tests.

Smoking, high BMI, and low physical activity are all known to increase the risk of microvascular complications and to affect the glycemic control in a negative way (101-103). Therefore these parameters were used to correct for confounders.

**The international cohort**

In studies III and IV, international quality diabetes register data from 2013 were used. In study III, data from six different registers, from eight countries, Denmark - the Danish National Diabetes Register (DanDiabKids), England and Wales - the National Paediatric Diabetes Audit (NPDA), Germany and Austria - the Prospective Diabetes Follow-up Register (DPV), Norway - the Norwegian Childhood Diabetes Register (NCDR), Sweden - the Swedish Pediatric Diabetes Quality Register (SWEDIABKIDS), and the USA - the T1D Exchange (T1DX), were included. In study IV, T1DX was not used due to the lack of HbA1c data during the first year after diagnosis.

These eight countries are all high-income countries with high standards of national health care (104).

Except for T1DX, which is clinically-based all registers are population-based with a high national coverage ratio of 80-98 %. The data from T1DX was based on 55 primary care centers for children with T1D. The care centers are spread across the United States (105). Although the patients came from the whole country the large majority of them were of non-Hispanic white race/ethnicity (NHW) which does not entirely reflect the actual demographic distribution in the US (105, 106), although NHW have a higher risk of being diagnosed with T1D than other race/ethnicity groups (107). White non-Hispanic patients are wealthier than other groups (108) and are also more likely to be insured (109) which could be one explanation for the skewed distribution in the T1DX.

In study III, 66,071 children with T1D fulfilled the inclusion criteria (< 18 years of age, HbA1c registered in year 2013, T1D duration > 3 months), while in study IV, the number was 55,194. The mean HbA1c in each country, in relation to age and T1D duration, was compared with the mean HbA1c in the other participating countries.

In study III, the population was divided into three different age groups, 0 to 9 years old, 10 to 14 years old and 15 to 17 years of age, which were estimates of a pre pubertal group, a pubertal group and a post pubertal group.
In study IV the population was divided into seven duration groups (3-<6 months, 6-<9 months, 9-<12 months, 1-<2 years, 2-<5 years, 5-<10 years and >10 years) to evaluate mean HbA1c early after onset with mean HbA1c with longer duration of T1D between the seven countries. HbA1c at diagnosis was not available in the dataset, so data on mean HbA1c at diagnosis in 2013 from each register was used as a proxy.

As seen in table 1 the number of patients varies between the countries, mostly due to different numbers of inhabitants in the participating countries. The proportion of males and females, T1D duration and age at diagnosis are nearly the same between the countries (Figure 4). The outcome measure was HbA1c related to actual age in 2013 and duration of T1D.

<table>
<thead>
<tr>
<th>Country</th>
<th>Austria</th>
<th>Denmark</th>
<th>Germany</th>
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<th>Sweden</th>
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<td>Patients</td>
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<td>HbA1c target value 2013 mmol/mol</td>
<td>53</td>
<td>55</td>
<td>58</td>
<td>58</td>
<td>&lt;58</td>
<td>52</td>
<td>&lt;6 years 69 6-12 years 64 &gt;13 years 58</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 1. Number of patients in each country and HbA1c target in each country in 2013.

Figure 4. Proportion of females, diabetes duration and age at onset of T1D in the participating countries in 2013.
STATISTICAL ANALYSES

SPSS 22® (SPSS Inc., Chicago, IL, USA) was used for the analyses in study I and SPSS 18® (SPSS Inc., Chicago, IL, USA) was used for the analyses in study II. SAS version 9.4 (SAS Institute, Cary, NC) was used for the analyses in studies III and IV.

Categorical data was analyzed with a Chi-square test.

A student’s T-test was used for parametric data, a Mann-Whitney U-test for non-parametric data and a Kruskal-Wallis test for more than two groups of non-parametric data.

Mean and standard deviation was used in all four studies for continuous variables.

In studies I and II a multivariate logistic regression was used to adjust for confounders.

Multiple linear regression was used both in the Swedish cohort and the international cohort to compare HbA1c between NDR and SWEDIABKIDS and between countries respectively and to adjust for potential confounders.

To make time-trends of HbA1c by TID duration and actual age visible, LOESS (locally weighted regression scatter plot smoothing) was used in studies III and IV.
ETHICAL ASPECTS

All four studies were approved by ethical committees. In the Swedish cohort the Linköping ethical board approved the studies and in the international cohort each country had ethical approval before sending data for analysis.

In studies I and II data were retrieved from SWEDIABKIDS and NDR in which the patients and their parents have given an informed consent before registration in the register. The patient can at all times redraw their consent without any further explanation, in line with the Declaration of Helsinki (110). All data analyzes in all four studies have been made on anonymous data.

In studies I and II center of registers in Västra Götaland made the data anonymous before start of the analysis.

In studies III and IV the national registers sent anonymous data to the University in Ulm where data has been kept and analyzed. No unanalyzed data has been allowed to leave Ulm University.

Due to the large number of patients in the studies and the anonymous data, the possibility of identification of a specific individual or harm to the privacy is considered to be very low.
RESULTS

The Swedish cohort

The main results in studies I and II were that good glycemic control during the teenage period was crucial to avoid complications related to T1D as a young adult and that females had a higher frequency of retinopathy than males 58 % and 53 % respectively as young adults (P <0.05).

Females had a higher mean HbA1c than males, 69 mmol/mol vs 66 mmol/mol, during adolescence, and were under-represented in the group < 57 mmol/mol during their teenage period (P < 0.01) (Figures 5a and 5b).

Figure 5a. Proportion of females vs males in SWEDIABKIDS with mean HbA1c < 57 mmol/mol during the teenage period ((Males N=591 (61 %), Females N=384 (39 %))
Figure 5b. Proportion of males and females in the whole study population (N=4250) ((Males N=2285 (54 %), Females N=1965 (46 %))

As seen in figure 6 the rate of complications is much higher with increasing HbA1c. Especially patients with poor glycemic control during the teenage period were at increased risk of complications as young adults.

Figure 6. Diabetes complications and smoking rate in NDR 2012 related to HBA1c (mmol/mol) in SWEDIABKIDS and NDR
Eighty-six percent of the patients who had mean HbA1c >78 mmol/mol in SWEDIABKIDS during the teenage period had retinopathy compared to the group with <57 mmol/mol in both SWEDIABKIDS and NDR where 27% had retinopathy. Seven percent had macroalbuminuria and 18% had microalbuminuria in the group with mean HbA1c >78 mmol/mol in both registers, in comparison with the group < 57 mmol/mol in both registers, where only four and two percent had micro- or macroalbuminuria respectively (P <0.01) (Figure 6).

Of the study population, nearly 2500 individuals were diagnosed before the age of 13 years. Twelve percent of them had mean HbA1c <57 mmol/mol in SWEDIABKIDS and 26% had mean HbA1c >78 mmol/mol during adolescence. In the group who were diagnosed at 13 years of age or older, 39% had mean HbA1c <57 mmol/mol and 14% had mean HbA1c >78 mmol/mol. In the group consisting of persons who were diagnosed before the age of 13 years, 57% had retinopathy both in 2011 and 2012, and in the group diagnosed during their teenage period, 29% had retinopathy on both occasions (P < 0.01). No such differences were seen in micro- and macroalbuminuria.

Adjusting for smoking, BMI, physical activity, duration and age at onset in a logistic regression, complications were still significantly more common in the group with higher mean HbA1c.

In the group with mean HbA1c > 78 mmol/mol in both registers, 39% were smokers compared to 9% in the group with good glycemic control in both registers (P < 0.01) (Figure 6). Fifty-two percent of smokers were females.

The international cohort
In studies III and IV there was a significant difference between countries in glycemic control measured as HbA1c both according to actual age and to diabetes duration.

As seen in figure 7, the mean HbA1c increased with increasing age of the T1D individuals in all countries. Mean HbA1c was 3-5 mmol/mol higher in the 10-14 years old group and 8 mmol/mol (7-9 mmol/mol) in the oldest age group compared to the 0-9 year old group in all participating countries. In all groups females had a higher mean HbA1c than males, and this was most pronounced in the oldest age group (Figure 8).

The mean HbA1c at diagnosis varied between 91 mmol/mol to 105 mmol/mol between the countries, and in all countries the mean HbA1c was about 50 mmol/mol (45-51 mmol/mol) lower three to six months after diagnosis (Figure 9). The mean HbA1c was then higher with longer duration, in all participating countries, with approximately 20 mmol/mol from the three to six months duration group to the 10-14 years duration group (Figure 9). As seen in figure 10, there are large differences in glycemic control among the countries and also the countries with good glycemic control soon after diagnosis have the best mean HbA1c with longer duration. The rise in mean HbA1c between the countries are virtually parallel (Figure 10).
Figure 7. HbA1c by age, including a non-parametric local regression of smoothing=LOESS

Figure 8. Mean HbA1c in males and females in the eight countries, and divided into three different age groups. (y=years, F=females, M=males)
Figure 9. Mean HbA1c at diagnosis in 2013 in the pediatric population with T1D in the participating registries, mean HbA1c in our study population at 3-<6 months, 9-<12 months and ≥10 years after diagnosis and the national target for HbA1c in each country in 2013.
Figure 10. HbA1c by duration, including a non-parametric local regression of smoothing (LOESS)
DISCUSSION

This thesis aimed to shed light on glycemic control in T1D patients, especially during adolescence, and on the implication of glycemic control on complications related to T1D. It also aimed to compare glycemic control among children and adolescents with T1D in high-income countries.

As in former studies (111, 112), females have worse glycemic control than males during childhood especially during adolescence. The same pattern was seen in both the Swedish and the international cohorts. The higher HbA1c among females is a possible explanation for the higher incidence of retinopathy seen in our cohort among females compared to males. Hormonal influence during puberty could explain the higher HbA1c in females. Maybe the fact that females enter puberty earlier than males could be another explanation; adults tend to see females as older than males at the same age and therefore give them more responsibility for their T1D treatment which they may not be ready to handle. A Finnish study has shown that females have a longer duration of diabetes symptoms before diagnosis than males and therefore higher HbA1c at diagnosis, and this could lead to a shorter remission period (35).

The teenagers with T1D who had mean HbA1c > 78 mmol/mol during their teenage period had a several times increased risk for complications, especially retinopathy, already as young adults even if they improved their HbA1c as young adults. For nephropathy persistent poor glycemic control seems to increase the risk for micro- and macroalbuminuria. Although good glycemic control is essential to reduce the risk for complications > 25% of the T1D patients with HbA1c < 57 mmol/mol had retinopathy and most of them were under the age of 30 years.

The teenage period is an important time in life and for teenagers with T1D it seems crucial to maintain good glycemic control to avoid complications.

The patients who were diagnosed before 13 years of age, had longer T1D duration and treatment regimens have improved over time which can be the explanation of their higher HbA1c compared to the individuals diagnosed after they turned 13 years. When adjusting for duration in regression models, HbA1c was still significant for the outcome of complication. Other factors that have an impact on glycemic control during childhood are socioeconomic differences (113), biological effects during puberty (114) and also differences in care and different setups of clinics (28, 115). Smoking, overweight and physical activity are other elements which influence the HbA1c and also the risk for complications. These are all factors that can be affected in a positive way by both healthcare professionals and the individual.

There is still no cure for diabetes and we cannot predict or affect the date of diagnosis but we can help the teenage patients to keep the HbA1c as near normal as possible and thereby keep the risk for complications to a minimum.
There were large differences in glycemic control in T1D patients, in all ages as well as in all durations of T1D, between countries. Despite the differences in glycemic control between countries the pattern of higher HbA1c with increasing age and duration was very similar. Our studies show an eight mmol/mol higher mean HbA1c from the youngest to the oldest age group and a higher mean HbA1c of approximately 20 mmol/mol in the group with > 10 years T1D duration compared with the three to six months duration group. Also a 50 mmol/mol reduction of HbA1c from diagnosis of T1D to three to six months after diagnosis was shown. These patterns were seen in all of the countries in our studies. Sweden had the lowest mean HbA1c in all age groups and in all duration groups but still had the same rise in HbA1c with increasing age and duration, but nevertheless there were complications related to T1D in Sweden. The countries with the lowest mean HbA1c at three to six months after diagnosis also had the best glycemic control after 10 years of T1D duration.

To learn from each other’s experiences, how other countries or other clinics achieve good T1D care like the QIC project in Sweden (28) is an opportunity through the registers. Benchmarking within and between countries is a way to improve T1D care (116). Without reinventing what others have already experienced, the overall goal, to treat children and adolescents with T1D in the best possible way, can be achieved.

To treat the T1D patients intensively directly after diagnosis, to treat the young T1D patients intensely and to decrease the rise in HbA1c with increasing age and duration of T1D is of the utmost importance to avoid complications early in life.
FUTURE PERSPECTIVE

Diabetes registers give an opportunity to share and compare results about T1D. To further develop the care of children and adolescents with T1D by sharing experiences and good examples seems crucial both within and between countries. To facilitate collaboration both nationally and internationally by shared meetings and using open access register data could improve the glycemic control and quality of life in young T1D patients. Also, to involve the young T1D patients and their families in the process seems important because they are the ones with the actual experience of living with T1D.

Early identification of T1D patients with risk of poor glycemic control is key. By retrospectively determining whether there are socioeconomic factors, genetic factors or auto-antibodies close to diagnosis that could predict later glycemic control we would be able to identify patients at risk of complications related to T1D.

The corresponding analysis could be of interest to predict the patients at risk of developing complications regardless of glycemic control.
SAMMANFATTNING PÅ SVENSKA


Incidensen av T1D varierar mycket mellan olika länder, högst incidens i världen finns i Finland följt av Sverige. I Sverige insjuknar varje år ca 900 barn och ungdomar under 18 år.

Målet med denna avhandling var att studera glukoskontroll, mått som HbA1c, hos barn och ungdomar med T1D i Sverige och relatera det till risken för komplikationer hos unga vuxna samt att jämföra glukoskontroll mellan länder.

I studie I och II användes nationella diabetesregistret, barn och ungdomar (SWEDIABKIDS) och nationella diabetesregistret, vuxna (NDR). Data på drygt 4000 unga vuxna med T1D och HbA1c i NDR åren 2011 och 2012 samt HbA1c (under tonåren) registrerat i SWEDIABKIDS användes. Risken att utveckla ögonkomplikationer (retinopati) redan som ung vuxen var många gånger högre för T1D patienter med dålig glukoskontroll speciellt under tonåren. Risken att utveckla njurkomplikationer relaterade till T1D (mikro- och makroalbuminuri) var ökad främst för dem med dålig glukoskontroll i båda registren. Kvinnor hade sämre glukoskontroll än män under tonårsperioden och en ökad risk för retinopati som unga vuxna jämfört med män.

I studie III och IV användes registerdata från åtta respektive sju länder (Danmark, England, Norge, Tyskland, Sverige, USA (Studie III), Wales och Österrike). I studierna analyserades data från ca 60 000 barn och ungdomar med T1D avseende hur medel HbA1c skiljde sig åt mellan de olika länderna. Studierna visade att det fanns stora skillnader i glukoskontroll hos patienterna med T1D mellan länderna både när det relaterades till ålder och T1D duration. Trots de stora skillnaderna mellan länderna avseende glukoskontroll var mönstret att HbA1c steg med stigande ålder och duration, nästan identiskt mellan länderna.
De fyra studierna visar att bra glukoskontroll är mycket viktigt för att undvika diabeteskomplikationer redan som ung vuxen och speciellt viktigt verkar det vara att hålla god kontroll under tonåren. Kvinnor har sämre glukoskontroll än män under tonåren och även mer retinopati som unga vuxna. Stora skillnader finns mellan västländer avseende glukoskontroll men i samtliga länder stiger HbA1c med ökande ålder och T1D duration på ett mycket likartat sätt.

Avhandlingen visar att det är viktigt att behandla T1D patienter intensivt direkt efter diagnos, behandla unga T1D patienter intensivt och minska ökningen i HbA1c med ökande ålder och duration av sjukdomen. På så sätt minskar risken för diabeteskomplikationer tidigt i livet. Diabetesregister gör det möjligt att jämföra resultat och dela erfarenheter både inom och mellan länder.

På detta sätt ökar vi möjligheten att ge T1D patienterna den bästa möjliga vården och minska risken för diabeteskomplikationer!
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Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

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Differences in glycemic control in type 1 diabetes children and adolescents in a national and international perspective and the effect on microvascular complications in young adults.

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