Institutionen för kliniska vetenskaper, 2025

Technology and Glucose Metabolic Control in Children and Adolescents with Type 1 Diabetes

Anna-Lena Fureman

UMEÅ UNIVERSITY

This work is protected by the Swedish Copyright Act (Act 1960:729)
ISBN: 978-91-8070-765-7 (print)
ISBN: 978-91-8070-766-4 (pdf)
ISSN: 0346-6612
Umeå University Medical Dissertations New Series no. 2378
Cover design by Alva Fureman
Electronic version available at: http://umu.diva-portal.org/
Printed by: Scandinavian Print Group, 2025

To my family

“Inne i dig öppnar sig valv bakom valv oändligt. Du blir aldrig färdig, och det är som det skall.”
Tomas Tranströmer

Ur dikten Romanska bågar: “För levande och döda” 1989

Table of contents

Abstract ... **3**

Abbreviations ... **5**

Enkel sammanfattning på svenska ... **6**

List of original papers ... **8**

Introduction ... **9**

Background ... **10**

Diabetes ... *10*
Acute complications ... 10
Long-term complications ... 11
Continuous subcutaneous insulin infusion (CSII) – Insulin pump treatment ... 11

Monitoring glycaemic control ... *13*
Capillary blood glucose monitoring (BGM) ... 13
Continuous glucose monitoring (CGM) ... 13
Real-time continuous glucose monitoring (rtCGM) ... 13
Intermittent scanning continuous glucose monitoring (isCGM) ... 14

Automated Insulin Delivery (AID) ... *14*

Glycaemic targets ... *15*
HbA1c ... 15
CGM metrics ... 15
Time in range (TIR) ... 15
Time in tight range (TITR) ... 15
Average sensor glucose (mean glucose value) and glycaemic variability (standard deviation, SD) ... 15

Partial remission (PR) ... *16*
C-peptide ... 17
Mixed-meal tolerance test (MMTT) ... 18
Definitions of partial remission (PR) ... 18
Insulin Dose Adjusted A1c (IDAA1c) ... 18
Clinical definition of partial remission (PR) ... 19

Overweight and obesity ... *19*
Puberty ... 20
The importance of insulin resistance ... 20
Puberty and adipose tissue ... 20
Long-term complications ... 20

Life with T1D ... *21*
Adolescence and T1D ... 21
Transition of responsibility ... 21
Psycho-social factors ... 21
Technology ... 21
Parental support ... 22
Communication ... 22
Remote control ... 22

Healthcare – the diabetes team 22
Quality registers *23*
Objectives **24**
Specific aims: *24*
Methods of analyses **25**
Data measurements *27*
HbA1c 27
Severe events 27
BMI-SDS 28
C-peptide 28
Study designs *29*
Quantitative data analyses *31*
Statistical methods 31
Qualitative data analyses *32*
Results **33**
Paper I, Comparing CSII – MDI *33*
Paper II, Comparing CGM and insulin delivery methods *35*
Paper III, Partial clinical remission *37*
Paper IV, Patients and parents' experiences of the new technology *38*
Discussion **39**
Insulin delivery method *39*
Glucose monitoring *42*
Partial remission *44*
Life with type 1 diabetes *45*
Strengths and limitations *48*
Conclusions **50**
Future perspectives **51**
Acknowledgements **52**
References **54**

Abstract

Background:
There has been a rapid technological development during the last decade concerning insulin pumps and continuous glucose monitoring (CGM) for children and adolescents with type 1 diabetes. Few studies have been performed on real-life data from children with type 1 diabetes to investigate the effects of such technological devices on glucose metabolic control and partial clinical remission.

Aim:
The aim of this thesis was to expand the understanding of what methods of insulin administration and glucose monitoring give the best opportunity to achieve good glucose metabolic control in children and adolescents with type 1 diabetes, and to explore the experiences of youths and parents using technological devices such as insulin pumps and CGM, the glucose target and the support from healthcare.

Methods:
Three of the studies were prospective, longitudinal, observational research with quantitative data from the Swedish National Diabetes Register (NDR-Swediabkids), and the Better Diabetes Diagnosis Study (BDD), where two include cross-sectional comparisons or cohort analysis (Papers I and II), and one is cross-linked with the BDD-register (Paper III). Papers I-III covered different time periods, i.e., Paper I 2011-2016, Paper II 2016-2023 and paper III 2007-2020. The fourth paper was an interview study with qualitative content analysis (Paper IV).

Results:
Overall, the use of insulin pumps and CGM-meters became increasingly common, where practically all children and adolescents with type 1 diabetes used CGM, most often in combination with an insulin pump by the end of the study period. In Paper I, we showed a small decrease of mean HbA1c (0.7-1.5 mmol/mol) without effects on the prevalence of reported hypoglycaemic events with insulin pump treatment compared to multiple daily injections. Insulin pump treatment was associated with female sex (OR: 1.30, 95% CI 1.16-1.45), higher BMI-SDS (OR: 1.13, 95% CI 1.07-1.19) and longer diabetes duration (OR: 1.16, 95% CI 1.14-1.18). In Paper II, the group with CGM and insulin pump had lower mean HbA1c compared with MDI treatment, 59.4 mmol/mol vs. 61.0 mmol/mol, $p<0.001$, but patients with rtCGM and MDI had the relatively largest reduction in HbA1c over time. There were associations between higher BMI and insulin pump use. In Paper III, we found that partial clinical remission was associated with insulin pump treatment (OR: 1.39, 95% CI 1.13-1.71), shorter diabetes duration (OR: 0.80, 95% CI 0.76- 0.84), and male sex (OR: 1.23, 95% CI 1.04-1.46). In Paper IV, the youths described increased satisfaction, security, freedom, and strengthened independence. The parents described improved sleep at night leading to increased quality of life. The opportunity for parents to follow their youth's glucose values from a distance does not seem to be a problem for neither youths nor parents, and the lowering

of the glucose target was not anything they had considered a problem. Both youths and parents had positive experiences of the diabetes teams, and parents emphasized the need of technical support and to stay connected during the transition period from childhood into adult life.

Conclusions:
New technologies facilitate life with type 1 diabetes for both youths and their parents, and CGM and insulin pump treatment improve glycaemic control, without substantial side-effects and seem to contribute to a longer period of partial remission. There are concerns regarding BMI-trajectories tied to the use of insulin pumps, particularly among teenagers, but from a user perspective, these devices confer improvements in quality of life, both for the adolescents using them and their parents. With the devices now being almost ubiquitous among paediatric patients, the diabetes teams will have to keep up with the rapid technological development to support the patients and their families as well as being vigilant to possible negative consequences of their use.

Abbreviations

AID	Automated Insulin Delivery
ATTD	Advanced Technologies & Treatments for Diabetes
BG	Blood Glucose
BMI	Body Mass Index
BMI-SDS	Body Mass Index Standard Deviation Score
CSII	Continuous Subcutaneous Insulin Infusion
CGM	Continuous Glucose Monitoring
DCCT	Diabetes Control and Complications Trial
DKA	Diabetes ketoacidosis
FDA	Federal Drug Administration
GH	Growth Hormone
HbA1c	Glycosylated Haemoglobin A1c
IDAA1c	Insulin Dose Adjusted HbA1c
IDF	International Diabetes Federation
IGF-1	Insulin-like Growth Factor-1
isCGM	Intermittent Scanning Continuous Glucose Monitoring
ISO	International Organization for Standardisation
ISPAD	International Society for Pediatric and Adolescent Diabetes
MDI	Multiple Daily Injections
MMTT	Mixed Meal Tolerance Test
NDR	The Swedish National Diabetes Register
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Care Excellence
PR	Partial Remission
RCT	Randomised Controlled Trial
rtCGM	Real Time Continuous Glucose Monitoring
SD	Standard Deviation
T1D	Type 1 Diabetes
TIR	Time In Range
TITR	Time In Tight Range

Enkel sammanfattning på svenska

I Sverige lever ca 8500 barn och ungdomar 0–17 år med typ 1 diabetes och omkring 900 insjuknar årligen. Sjukdomen typ 1 diabetes beror på att kroppen inte kan tillverka det livsnödvändiga hormonet insulin. Därför måste man tillföra insulin med flera injektioner i underhudsfettet dagligen via en insulinpenna eller via en insulinpump.

För högt blodsocker medför risk för komplikationer som t.ex. hjärt-kärlsjukdomar, njursjukdom, nerv- och ögonskador. För lågt blodsocker medför risk för medvetslöshet och kramper. Blodsockret måste därför mätas flera gånger per dygn via ett stick i fingret för att styra behandlingen. Det senaste decenniet har utvecklingen av tekniska hjälpmedel gått snabbt och möjligheten att registrera glukosvärdet kontinuerligt via en sensor i underhudsfettet på armen eller magen som sedan skickar dessa värden till en handenhet, mobiltelefon eller insulinpump har revolutionerat egenvården för patienter med typ 1 diabetes.

Efter diagnos av typ 1 diabetes då kroppen tillförs insulin återhämtar sig en del av bukspottkörtelns insulinproducerande celler (betaceller) och kroppen blir mer känslig för insulin, vilket leder till att insulinbehovet minskar tillfälligt och man kan komma in i s.k. smekmånads fas (partiell remission). Med ett blodprov (C-peptid) kan man mäta hur mycket egen produktion av insulin kroppen har kvar och forskning har visat att en kvarvarande nivå av C-peptid minskar risken för sena komplikationer av typ 1 diabetes.

Kontinuerlig glukosmätning (CGM) har även möjliggjort för föräldrar att följa sitt barns glukosvärde i sina mobiltelefoner och ha larmfunktioner som signalerar när glukosvärdet riskerar att bli för högt eller lågt. Denna möjlighet kan innebära en ökad trygghet, men ev. också en stress t.ex. för föräldrar som är på arbetet eller ungdomar med typ 1 diabetes, som behöver ta ett större eget ansvar för sin sjukdom inför vuxen blivandet.

Syftet med denna avhandling är att öka förståelsen av vilka insulin metoder och glukosmonitorering som kan ge bäst förutsättningar att uppnå en god glykemisk kontroll samt att utforska ungdomar med typ 1 diabetes och deras föräldrars upplevelse av den nya tekniken (insulinpump och CGM) samt stödet från sjukvården.

Denna avhandling består av tre registerbaserade observationsstudier och en kvalitativ intervjustudie.

I studie I såg vi att behandling med insulinpump gav en förbättrad glukoskontroll (med ett lite lägre HbA1c värde) jämfört med behandling med insulinpenna.

I studie II visade vi att kontinuerlig glukosmätning (CGM) och insulinpump gav förutsättningar att uppnå glukosmålet i större utsträckning än CGM och insulinpenna, men de med CGM och insulinpenna hade den relativt sett största minskningen av HbA1c vilket innebär att de med insulinpenna har störst nytta av CGM.

I studie III visade vi att de yngsta barnen och flickor hade lägst chans att komma in i partiell remission, men att behandling med insulinpump verkar öka frekvensen och även förlänga perioden.

I studie IV visade vi att ungdomar med typ 1 diabetes och deras föräldrar är nöjda med den nya tekniken och med stödet från diabetesteamet. Varken ungdomar eller föräldrar upplever att möjligheten för närstående att följa glukosvärdet via en mobiltelefon är något problem utan det upplevs snarare som en trygghet.

Sammanfattningsvis visar studierna att den nya tekniken underlättar livet och förbättrar glukoskontrollen för barn och ungdomar med typ 1 diabetes och deras föräldrar utan negativa sidoeffekter. Det är viktigt att utvecklingen av automatiska insulinpumpar (AID) fortsätter vilket kommer att förenkla vardagslivet för familjerna ytterligare.

List of original papers

This thesis is based on the following papers, referred to as Study I, II, III and IV.

I. Fureman AL, Lilja M, Lind T, Särnblad S, Bladh M, Samuelsson U. Comparing subcutaneous insulin infusion and multiple daily injections in children with Type 1 diabetes in Sweden from 2011 to 2016-A longitudinal study from the Swedish National Quality Register (SWEDIABKIDS). *Pediatric Diabetes* 2021;22:766-775.

II. Fureman AL, Bladh M, Lilja M, Samuelsson U, Särnblad S, Lind T. Comparing continuous glucose monitoring with insulin pump or multiple daily injections in children with Type 1 diabetes in Sweden from 2016 to 2023-A longitudinal study from the Swedish National Diabetes Register (NDR-Swediabkids). *Manuscript*.

III. Fureman AL, Bladh M, Carlsson A, Forsander G, Lilja M, Ludvigsson J, Samuelsson U, Särnblad S, Lind T. Partial Clinical Remission of Type 1 Diabetes in Swedish Children: A Longitudinal Study from the Swedish National Quality Register (SWEDIABKIDS) and the Better Diabetes Diagnosis (BDD) Study. *Diabetes Technology & Therapeutics* 2024;26(11):851-861.

IV. Fureman AL, Lind T, Lilja M, Särnblad S, Samuelsson U, Sjöström R. Youths with type 1 diabetes' and their parents' experiences of insulin pumps and continuous glucose monitoring. *Submitted*.

Paper I and III are reprinted with permission from the publisher.

Introduction

In 2024, it was estimated that over 1,8 million children and adolescents (0-19 years) worldwide were living with type 1 diabetes (T1D), and a further 219,000 children developed the disease annually, with Europe having the highest prevalence [1]. In Sweden, there are around 8,500 children and adolescents between 0 and 17 years of age living with T1D and around 900 children and adolescents develop T1D annually, corresponding to an annual incidence of 44/100,000 [2]. Treatment consists of either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) [3], and today CSII is the most physiological way to deliver insulin [4]. In 2016, 44% of children and adolescents with type 1 diabetes in Europe were treated with CSII [5] and in Sweden this number was 61% further increasing to 85% in 2024 [6].

The introduction of continuous glucose monitoring (CGM) a decade ago has improved the opportunity to reach the target for glucose control and has decreased the risk of hypoglycaemia [7]. This technological evolution of insulin delivery and glucose monitoring systems have had an enormous effect on the management of diabetes and thus enabled a lowering of the glucose targets.

The target in Swedish guidelines for HbA1c has been ≤48 mmol/mol since 2017 [8], which is consistent with recommendations from the National Institute for Care Excellence (NICE) [9]. In 2024, the International Society for Pediatric and Adolescent Diabetes (ISPAD) also lowered their recommended target for HbA1c to ≤48 mmol/mol for those who can safely reach that target with the support of advanced technologies (CGM and automated insulin delivery (AID) systems) and ≤53 mmol/mol in all other scenarios [10]. In Sweden, ”Time in tight range” (TITR) i.e., 3.9-7.8 mmol/L is the CGM target [8], and the mean value for HbA1c has decreased in recent years to internationally low levels in all paediatric age groups and in 2024 it was 51.9 mmol/mol [6].

The Diabetes Control and Complications Trial (DCCT) and follow-up data clearly indicate that poor glycaemic control during adolescence and young adulthood increases the risks of micro- and macrovascular complications later in life [11,12]. The Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated, 30 years after the DCCT study, that intensive diabetes treatment decreases the incidence of cardiovascular disease [13]. Therefore, the development of technical devices and proper usage is important to improve the glucometabolic control to decrease the risks of long-term complications.

Background

Diabetes

Diabetes mellitus is characterized by hyperglycaemia, defined as fasting plasma glucose ≥7.0 mmol/L or random plasma glucose ≥11.1 mmol/L [8]. Type 1 diabetes (T1D) is caused by an autoimmune process destroying the insulin-producing pancreatic β-cells, resulting in loss of endogenous insulin production. This leads to relative insulin deficit that progresses to absolute insulin deficit, increased plasma glucose levels, intracellular starvation, and ketonaemia [14].

There is no effective cure available and untreated the disease causes death from ketoacidosis. Treatment consists of substituting insulin by subcutaneous injections five to six times daily (MDI) or via CSII with an insulin pump. The goal of the treatment is to mimic physiological insulin secretion to restore normal metabolism and achieve glycaemic control which means a constant striving for normoglycaemia. Data from people without diabetes highlight the exquisite regulation afforded by endogenous insulin production with mean glucose being 5.4-5.5 mmol/L and 96% of time with values corresponding to TITR in diabetes [15].

This disease presents challenges to everyday life with a need for daily insulin injections, glucose testing, regular meals, and regular physical activity to keep the blood glucose well balanced. In addition, poor metabolic control during adolescence increases the risk of severe complications later in life [11,12]. Even people with well-controlled T1D have a doubled risk of death from any cause as well as from cardiovascular causes compared to the general population, and the risks are several times higher among patients with poor glycaemic control [16].

Acute complications

According to current guidelines from ISPAD, hypoglycaemia is defined as plasma glucose ≤3.9 mmol/L and children with T1D should spend less than 4% of their time below this level [17]. A study with CGM in healthy children without T1D (8-15 years) showed that they had glucose levels ≤3.9 mmol/L for 2.0% of the time [18]. Fear of hypoglycaemia are major physiological and psychological barriers to achieving optimal glycaemic control [19], and may result in significant psychological stress for children with T1D and their caregivers [20]. This may lead patients and/or parents to accept higher glucose levels to avoid hypoglycaemia which can lead to increased HbA1c levels contributing to an increase in long-term complications [21].

Severe hypoglycaemia is defined as an event with severe cognitive impairment (including convulsions or coma) requiring assistance by another person to administer carbohydrates, glucagon, or intravenous glucose [22]. Hypoglycaemic coma is a subgroup of severe hypoglycaemia defined as an event associated with a seizure or loss of

consciousness [23]. The incidence of hypoglycaemic coma has decreased over the last two decades and international registries from developed countries shows a current rate of 3 to 7 per 100 patient-years [17]. Concern has been raised that lower HbA1c levels are associated as a risk factor for severe hypoglycaemia and that this is important to study [24].

The autoimmune destruction of the pancreatic β-cells leads to insulin deficit and intracellular starvation which stimulates production of ketones by the liver from visceral fat. The ketones in the blood decreases pH and leads to acidosis. Diabetic ketoacidosis is defined as hyperglycaemia (plasma glucose >11 mmol/L), venous pH <7.3 or serum-bicarbonate <18 mmol/L, and ketonaemia (blood β-hydroxybutyrate ≥3.0 mmol/L) [25]. Around 27% of all newly diagnosed children with T1D in Sweden has ketoacidosis and among the youngest children (<2 years) this number is 55% at diagnosis [6]. In 2024, the frequency of ketoacidosis among children and adolescents with T1D in Sweden was 0.8% [6]. Since there has been concern whether CSII may contribute to increase the risk of ketoacidosis this is of interest to explore [26].

Long-term complications

The long-term vascular complications of diabetes include retinopathy, diabetic kidney disease, neuropathy, and macrovascular diseases. Microvascular complications of diabetes are extremely rare before puberty.

However, early functional and structural abnormalities may be present a few years after the onset of T1D [27]. There is a strong association between a child's HbA1c level as early as 3-15 months after diagnosis and HbA1c level and complication status in adulthood [28].

Macrovascular complications with cardiovascular disease, such as myocardial infarction and stroke, is the leading cause of death in people with diabetes as well as in the general population [29]. Atherosclerosis starts early in life, and this process is more pronounced in children with T1D than in healthy children [30-32]. Diabetes is associated with a tenfold increase in the risk of cardiovascular disease [33], and especially women with diabetes have a much higher risk compared to healthy women [33].
Given that the pathophysiological process of microvascular complications starts early in children with T1D and accelerates during puberty, it is essential to aim for normoglycaemia already from the time of diagnosis. A question that has been raised is whether technical devices and intensive insulin therapy can promote a better glycaemic control leading to a decreased risk of long-term complications [34].

Continuous subcutaneous insulin infusion (CSII) – Insulin pump treatment

More than 45 years ago, CSII was introduced to achieve a better glycaemic control [3,35]. A basal rate of insulin is automatically infused by the insulin pump in a pre-programmed pattern. For carbohydrate meals or when glucose levels are above target, a bolus dose can be delivered manually [36]. The indications in the Swedish national guidelines for

initiating CSII treatment are broad [8]. This has led to a large variation in frequency of usage between different counties and paediatric clinics in Sweden with frequencies ranging from 39% to 94% [2]. These differences remain largely unexplained. Also, there is no correlation between achieved mean HbA1c and frequency of usage of insulin pumps at the different paediatric clinics [2]. The use of CSII has increased among children and adolescents with T1D in Sweden during the last decade, where 49% were using CSII in 2013, which in 2023 had increased to 82% [2]. Although treatment with CSII is associated with increased costs compared with MDI [37], some studies have shown that CSII is cost-effective when it results in improved quality of life (QoL) and improved glycaemic control [38-40]. It still remains to be studied which individuals with T1D who would benefit the most from CSII treatment, where previous studies have shown that individuals with poorer metabolic control benefit the most from improved glycaemic control [16], and potentially insulin pump treatment. For example, teenage girls with T1D have been shown to have poorer metabolic control compared to boys and suffer more from complications in young adulthood [41], and therefore they would benefit more from CSII treatment.

In randomised controlled trials [42], CSII among adolescents and adults with T1D has been demonstrated to improve metabolic control by lowering HbA1c and decrease complications [43]. In young children, CSII reduces the incidence of severe hypoglycaemic events [44] which is an important feature of its use in this age group [45,46]. However, in terms of efficacy, studies show varying results regarding the ability of CSII to obtain or sustain lower HbA1c levels after the first 6-12 months of use [47-49]. Previous studies in Sweden have given somewhat different results concerning the efficacy of CSII. In 2008, Skogsberg et al could not show better metabolic control with CSII compared to MDI [50], although they reported improved treatment satisfaction. In another follow-up of patients who started CSII treatment in the years 2005-2009 compared to matched controls, CSII treatment improved the metabolic control during the first year but not thereafter. The group with CSII treatment had fewer incidents of severe hypoglycaemia during follow-up but the number of ketoacidosis increased [51].

Using real life data and observational studies to supplement randomised controlled trials (RCT) supplements the findings from the RCTs and allows for comparisons when the devices are used as everyday tools to answer questions regarding their efficacy in improving glycaemic control.

Insulin pump related adverse events are relatively common and include infusion set failures, which can lead to interrupted insulin delivery and increasing the risk of diabetes ketoacidosis (DKA) [52-56]. Another frequently encountered issue is lipohypertrophy, or local fat accumulation at the site of insulin administration [57]. Lipoatrophy, fat loss at the site of prior insulin infusion sites, is less common but more often observed in patients with multiple autoimmune conditions [58]. Skin irritations are frequently observed after repeated exposures to adhesives from medical devices and studies have demonstrated that localized eczematous reactions at the site of infusion cannula insertion are common [59,60]. In young children with sensitive skin, this can be the reason why they must cease with CSII treatment or CGM usage.

Monitoring glycaemic control

Capillary blood glucose monitoring (BGM)

Self-monitoring with capillary measurements of blood glucose (BG) in everyday life was introduced in the 1980's as a cornerstone of insulin treatment. The frequency of BG testing is linked to improved HbA1c levels and a decrease in acute complications [61-64]. Children and adolescents are recommended to test BG 6 -10 times per day [65]. The precision of the BG meters is ±15% (or ±0.83 mmol/L if plasma glucose <5.6 mmol/L), which is now judged as acceptable according to ISO standard 15197:2013 [66]. Data from glucometers can be uploaded into a computer and used for retrospective analysis of glycaemic control, but the disadvantages are that testing interrupts other activities and that it only gives a snapshot of the current situation with no information about the blood glucose levels between testing points.

Continuous glucose monitoring (CGM)

Over the last 20 years glucose monitoring has progressed from capillary blood glucose fingersticks to the implementation of newer systems for CGM based on subcutaneously placed glucose sensors for interstitial fluid. The first device was approved by the US Food and Drug Administration (FDA) in 1998. The first device collected glucose values over three days and data could be transferred to a receiver through a cable, uploaded to a computer and analysed afterwards by the diabetes team and patient. Today, these CGM systems have advanced and are wireless, provide direct information on current glucose levels and have become the standard of care for T1D in many countries [67].
The CGM sensors commercially available today use electrochemical methods, particularly glucose oxidase – based technology to measure interstitial glucose. Minimally invasive CGM sensors with a wearing duration of 7-14 days and designed for transdermal self-application are available for children and adolescents [65].
The devices can be categorized into real time (rtCGM) and intermittent scanning (isCGM) CGMs.

Real-time continuous glucose monitoring (rtCGM)

The rtCGM systems automatically transfer glucose data from the sensor applied to the subcutaneous fat on the overarm, stomach, or buttock, and display the glucose values to an insulin pump, a smartphone or a receiver. Sensor data can be transmitted to a cloud-based server in real time which makes it accessible for remote monitoring by relatives and caregivers.

Intermittent scanning continuous glucose monitoring (isCGM)

isCGM, also called flash CGM, does not automatically make glucose levels available to the user but by scanning the arm worn sensor with a smartphone or a handheld device the values are instantly accessed and enables 8 hours retrospective data.

Both isCGM and rtCGM have adjustable alarms that becomes activated when the glucose level is low or high. They also indicate the direction of change of the glucose levels by arrows on the smartphone's handheld monitors, or insulin pump's display which enables the patient or the parents to intervene to avoid hypo- or hyperglycaemia.

These technologies have improved the ability to maintain stable glucose levels, increasing the proportion of time spent in the target range 3.9-10 mmol/L and reducing the risk of hypoglycaemia <4 mmol/L [7,68-71].

The indications for prescribing a CGM device according to the Swedish Association of Paediatric Endocrinology and Diabetes (SFPED) in 2016 was young age, frequent episodes with severe hypoglycaemias and difficulties achieving a good metabolic control with capillary fingersticks. The use of rtCGM and isCGM has since then become more prevalent, with an increase from 78% in 2016 to 98% in 2023 [2]. However, there is a difference in cost between the systems, and it is of interest to investigate if they have benefits compared to each other, and which combination of insulin delivery method that have the best glycaemic outcome.

Automated Insulin Delivery (AID)

AID implies integrating continuous glucose monitoring (CGM) with an insulin pump using algorithms to adjust insulin delivery in response to sensor glucose data, also referred to as closed loop or artificial pancreas systems. The use of AID is increasing in all age groups [72,73] and recent meta-analyses comparing AID to other treatment modalities showed benefits in HbA1c and time in range [74,75].

In Sweden, the use of AID pumps has increased rapidly and the frequency was 54% in 2024 with a large variation between different paediatric clinics with frequencies ranging from 11% to 89% [6]. Again, there was no correlation between achieved mean HbA1c and frequency of usage of AID in these different paediatric clinics [6].

The latest advanced hybrid closed-loop insulin pumps (AID) where the rtCGM is integrated with the pump can by algorithms give extra insulin when the glucose level is rising and stop insulin delivery when the glucose level is falling. This technique has facilitated everyday life for patients with T1D and their parents, but it also challenges them and the diabetes team when it comes to using the technology in the intended way [76]. Therefore, it is important to investigate how they experience the new technology and the support from the diabetes team to improve the education, communication and ways of supporting them to increase adherence with treatment and decrease potential adverse effects.

Glycaemic targets

HbA1c

Glucose can freely enter erythrocytes and react non-enzymatically with the β-chain of haemoglobin A to form HbA1c. This process is driven by the concentration of glucose and the proportion of HbA1c to HbA (measured in mmol/mol or percent) thus reflects mean glycaemia during the maximum 120-day lifespan of the erythrocyte [77].
HbA1c has long been the accepted benchmark for glycaemia and was used to investigate the importance of glycaemic control in the DCCT/EDIC study [78]. It was shown that HbA1c as a marker of glycaemic control was strongly associated with the risk of diabetes complications. However, it has several limitations, such as a wide range of mean glucose concentration values for a given HbA1c [79], and unreliable measurements in certain conditions including anaemia and hemoglobinopathies [80].

CGM metrics

Time in range (TIR)

The concept “Time in range” was introduced in clinical diabetes care around 2017 and was more formally accepted after the consensus document from an expert group at Advanced Technologies & Treatments for Diabetes (ATTD) in 2019 [81].
It is recognized that time spent in range 3.9-10 mmol/L may need to be >80% to achieve an optimal HbA1c target of ≤48 mmol/mol [10].

Time in tight range (TITR)

In Sweden, “Time in tight range” 3.9-7.8 mmol/L is used in paediatrics as continuous glucose monitoring target [8,82], and TITR >55% might be needed to reach the goal for HbA1c ≤48 mmol/mol [83]. Increasing time spent in tight range may reflect lower glucose variability and reduce the long-term risk of complications and therefore it has been suggested as a new metric to characterize optimal glycaemia [84,85].

Average sensor glucose (mean glucose value) and glycaemic variability (standard deviation, SD)

These are metrics included in standardized CGM reports that could be especially relevant in situations where CGM data are easier to obtain than an HbA1c, for instance in telemedicine. Average sensor glucose is strongly correlated to HbA1c and associated with the risk of microvascular complications, and glycaemic variability can predict hypoglycaemia [86]. Time spent in range <4 mmol/L should not exceed 4% and time spent <3 mmol/L need to be less than 1% to avoid events with severe hypoglycaemia [10].

Partial remission (PR)

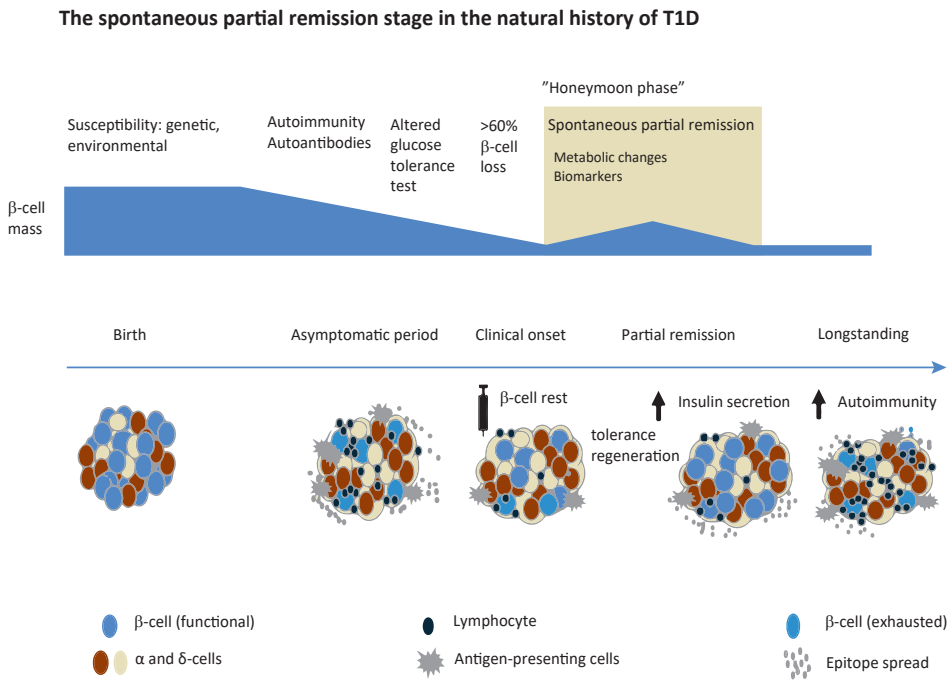


Figure 1. Remission phase in paediatric type 1 diabetes. Redrawn and adapted from Fonolleda, M, et al. [87], Copyright © 2017 Karger Publishers, Basel, Switzerland.

In most children and adolescents diagnosed with T1D, the need for insulin decreases temporarily when insulin treatment is started [88]. This is due to a partial recovery of the β-cells with increased insulin secretion and an increased peripheral insulin sensitivity before insulin production decreases again [89,90]. The remission period, often referred to as the "honeymoon phase", can last for weeks to several years and is characterized by stable glucose levels within the normal range despite variations in diet and physical activity [91,92]. The term partial remission is used instead of remission, because there is never a complete remission in T1D which is a chronic disease.

C-peptide

In 1967 it was discovered that proinsulin and C-peptide were involved in the biosynthesis of insulin [93]. Proinsulin is a polypeptide, synthesized in the β-cells of the islets of Langerhans in the pancreas. After cleavage of proinsulin, C-peptide (a 31-amino-acid-peptide) and endogenous insulin are produced in equal amounts and co-secreted into the blood.

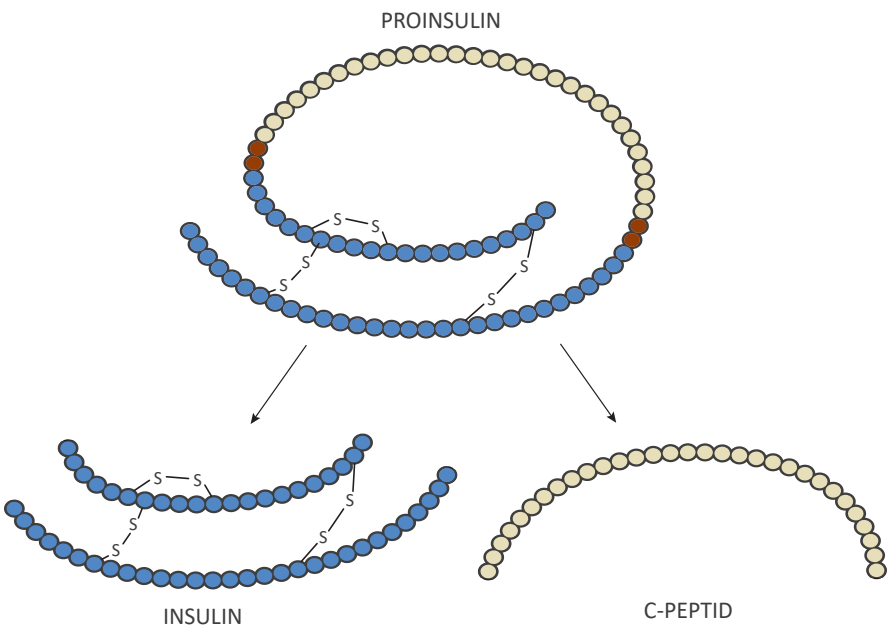


Figure 2. Illustration of proinsulin, insulin and C-peptide.

C-peptide has a longer half-life (20-30 min) compared to endogenous insulin (3-5 min), and unlike insulin experiences little first pass clearance by the liver and is therefore a better marker of residual β-cell function compared to insulin [94]. C-peptide is metabolized by the kidneys and cleared from the circulation at a constant rate in contrast to insulin. By measuring C-peptide concentrations in patients with newly diagnosed T1D it was shown already in the 1970's that they had preserved β-cell function during the first two years of the disease and then it decreased thereafter especially in patients with early onset [95]. The C-peptide secretion declines by each year after T1D onset [96-99], but can still be detected in individuals decades after their diagnosis [100-103]. C-peptide seems to have physiological properties on its own, for example, to

improve the microvascular blood flow and endothelial function through the release of endothelial nitric oxide [104,105]. The lack of C-peptide secretion might contribute to microvascular blood flow abnormalities to a larger extent than decreased insulin secretion or increased blood glucose levels [106]. Previous studies have analysed factors that affect the course of T1D during the first years after onset and they have shown that ketoacidosis, young age, and infection at onset reduce the likelihood of a partial remission phase [107-109]. At present, there is no treatment available in Sweden that can restore β-cell function for an extended time, but it is still important to try to preserve as much β-cell performance as possible as studies have shown that it reduces the risk of developing vascular complications and severe hypoglycaemia [110,111]. However, there is a new therapy with monoclonal anti-CD3 antibodies (teplizumab) that has been authorized by the Federal Drug Administration (FDA) in the United States in 2022 for the treatment of individuals with multiple autoantibodies, and T1D in stage 2 which means having ≥2 autoantibodies, abnormal blood sugar but no symptoms [112]. Studies have shown that teplizumab treatment may preserve some residual β-cell function for several years [113]. This treatment is not yet approved in Europe.

Mixed-meal tolerance test (MMTT)

The gold-standard measure of endogenous insulin secretion in T1D is drinking a liquid meal beverage that contains fats, protein and carbohydrates to stimulate C-peptide secretion as a standardized MMTT area under the curve C-peptide (AUC CP) [94]**.** This is a test predominantly used in research since it is time consuming with blood samples taken every 30 minute for 2 hours to allow measurement of area under the curve (AUC) and peak C-peptide [114].

Definitions of partial remission (PR)

It has been difficult to compare studies of partial clinical remission since there have been many different definitions [92,108,115-119]. Since disease-modifying therapies now are coming, there is a need of comparable data, and in 2009 Mortensen et al presented the internationally accepted definition insulin dose-adjusted HbA1c (IDAA1c) [116].

Insulin Dose Adjusted A1c (IDAA1c)

In 2009, Mortensen and the Hvidøre Study group on Childhood Diabetes presented a new definition for partial remission for children and adolescents with T1D [116]. The study was a multicentre longitudinal investigation in 18 paediatric departments in 15 countries in Europe and Japan in 1999-2000, including 275 patients (0-16 years) with newly diagnosed T1D. They were followed from onset of T1D, and stimulated C-peptide with MMTT was used as a measure of residual β-cell function after 1, 6, and 12 months. By multiple regression analysis, they demonstrated a negative association between stimulated C-peptide and HbA1c (regression coefficient -0.21, $p<0.0019$) and insulin dose (-0.94, $p<0.001$). These results suggested the definition of an insulin dose-adjusted

A1c (IDAA1c) as: HbA1c (%) + [4 x total daily dose of insulin (U/kg/day)] ≤9 since a calculated IDAA1c value ≤9 corresponds to a predicted stimulated C-peptide >0.3 nmol/L and this had a significantly higher agreement ($p<0.001$) with residual β-cell function than use of a definition of HbA1c ≤58 mmol/mol [116].

Clinical definition of partial remission (PR)

The definition of PR in the Swedish guidelines in 2008, and commonly used in clinical practice in many countries [120] is total daily insulin dose <0.5 U/kg/day and HbA1c <57 mmol/mol, as this was the target for HbA1c during this time period [121].

There are limitations using HbA1c or IDAA1c to define partial remission as it can be difficult for patients having a very high HbA1c at diagnosis of T1D to reach HbA1c <57 mmol/mol 3 months after diagnosis even though they are in partial remission with a very low total insulin dose.

Measuring C-peptide at diagnosis of T1D before the first insulin dose is administered is part of a clinical routine in Sweden since it is one of the blood samples collected in the Better Diabetes Diagnosis Study (BDD) [122]. However, after diagnosis there are few paediatric clinics that measure C-peptide during follow-up visits.

Overweight and obesity

Overweight and obesity in children and adolescents is a growing problem in society as well as in the group of children and adolescents with T1D. Obesity is a significant global health threat for both adults and children being a chronic low-grade inflammatory disease represented by multifactorial dysfunctions [123]. Previous studies have demonstrated that there is a link between obesity in childhood and adolescence with an increased T1D incidence [124,125]. A high linear growth is associated with an increased risk of T1D in childhood [126]. Among adolescents (16 to 19 years) higher Body Mass Index (BMI) percentiles are associated with an approximately 25% increased risk for incident T1D for each incremental standard deviation (SD) in BMI [125].
During periods of rapid growth in the childhood, there is a higher demand of insulin secretion from the β-cell and at the same time insulin is in a complex interaction with other hormones such as insulin-like growth factor 1 (IGF-1) and growth hormone (GH), which are known to increase the peripheral insulin resistance [127]. In paediatrics BMI-SDS refers to standard deviation scores of BMI to help assess a child's BMI relative to other children of the same age and sex, indicating whether their BMI is within the normal range, or if they are underweight, overweight or obese [128].

Puberty

The importance of insulin resistance

Insulin sensitivity decreases during puberty, and this is probably restricted to glucose metabolism, resulting in hyperinsulinaemia that amplifies the effect of insulin on protein metabolism and facilitates linear growth [129,130]. The increase in insulin secretion during puberty following induction of hyperglycaemia is two to three fold higher in adolescents compared to prepubertal children or adults [131]. A sex difference has frequently been described with lower insulin sensitivity in girls which may reflect differences in sex steroids and GH levels [132,133]. Insulin sensitivity is even more impaired in adolescents with T1D than in healthy adolescents [130,134,135] and girls are more insulin-resistant than boys [136]. Decreased insulin sensitivity has been associated with elevated GH levels [134,137] and a disturbed GH/IGF-1 axis has been suggested as a cause of this increased insulin resistance in adolescents with T1D [138].

Puberty and adipose tissue

During puberty total fat mass increases in both sexes. However, since girls have a much lower gain in lean body mass it is only girls that show an increase in percentage body fat. At the end of puberty, the proportion of body fat in boys are approximately 10% compared to 20-25% in girls [139]. The sex difference in the change of lean body mass during puberty is caused by differences in androgen levels, although differences in physical activity might also be an important mediator [140]. The annual year report from NDR-Swediabkids 2023 showed that girls with T1D are less physically active compared to boys [2].

Long-term complications

Obesity increases cardiovascular risk factors in children with T1D [141-144], it causes changes in sex hormones in puberty [145], increases the risk of non-alcoholic fatty liver disease [146], and may reduce health-related quality of life, and increase the risk of psychosocial problems [147,148]. Particularly girls with T1D are at risk of excessive weight gain [41,149,150], and teenage girls with excessive weight gain are shown to have an increased risk of complications in adulthood [41] and premature death [151].

The problematic long-term trend of continuous excessive weight gain in children and adolescents with T1D has been related to intensified insulin therapy, insulin method, and glycaemic control [149,152-155], and studies have shown BMI-SDS being inversely associated with HbA1c [71]. It is therefore important to find the technology that can achieve a better glycaemic control without an increase in BMI-SDS.

Life with T1D

Adolescence and T1D

Adolescence is a time of rapid physical, psychological, and emotional changes. During this period, it is necessary to become an independent individual, to rely on one-self, and develop one's own identity. The adolescent has to develop a new relationship to his/her parents, be able to have close relationships with individuals outside the family, develop a life-style and self-care, consider how to live life as an adult, and plan a career [156].

Having T1D, adolescence is also a period when glycaemic control commonly deteriorates [157]. This depends on a combination of non-modifiable factors such as the effect of gonadal steroids, a rise in lean body mass leading to increased insulin requirements, physiological insulin resistance, and modifiable factors such as behavioural and psychosocial changes leading to reduced adherence with treatment regimens together with a decline in physical activity [158,159].

Transition of responsibility

Being a teenager with T1D involves additional challenges when responsibilities for insulin therapy, self-monitoring and meal planning must move from the parents to the teenager himself. Adolescents have described constantly struggling with diabetes self-management, dealing with hyper- and hypoglycaemia, as well as fear of complications later in life. They describe a fear of nocturnal hypoglycaemia and anxiety about the risk of dying in their sleep. They are aware of diabetes as a chronic illness and that they have to live their lives in a new way – a life with T1D [160].

Psycho-social factors

During adolescence there is also a large rise in mental health issues such as anxiety, depression, and eating disorders [161]. Disordered eating behaviours are common in adolescent girls with T1D, but not in boys and have been associated with poor glycaemic control [162-167], an increased risk for microvascular complications [163,168], high BMI [169,170], and reduced adherence to insulin therapy [165]. Omission of insulin has been associated with poor glycaemic control [171], and studies have revealed that approximately 10-15% of adolescent girls have been reported to reduce their insulin dosage in an attempt to lose weight [163,165,166,172].

Technology

Even though new technology with CGM and AID has arrived with the potential for improved adherence to treatment, there is yet no evidence of better diabetes-related outcomes for adolescents [173]. The annual report 2023 from the Swedish National

Diabetes Register (NDR) showed that there is an increase in mean HbA1c in adolescents and young adults, 19 to 23 years of age, illustrating the need for better support and a more individualised transition into adult healthcare [2].

Parental support

It has been shown that parental involvement and shared diabetes self-management are important during adolescence [173-177]. It is known that relations between adolescents and parents are of great importance to diabetes self-management, and several studies indicate an association between family conflicts and glycaemic control [178-184].

Adolescents with parents who were perceived to be over-involved in diabetes care have worse glycaemic control, and the greater the disagreement between parents and adolescent regarding responsibility for diabetes self-management, the worse glycaemic outcome [185]. Having a child who develops T1D implies an enormous strain on the family system and increases the risk of exhaustion depression in the mothers [186].

Communication

An empathic, authoritative parenting style with realistic and clear expectations are correlated with better glycaemic control and paternal involvement is important [187]. Autonomy-supportive communication is related to improved adherence [188], whereas negative parental tones in discussions about diabetes was associated with worse glycaemic control [179].

Remote control

The new technology implies the ability for parents to monitor their child's glucose levels via a mobile phone and also provides the opportunity to have alarms when the glucose level is too high or low [189] which can provide parents with a feeling of security, potentially leading to improved sleep quality. However, this constant monitoring could also lead to increased stress, as parents may frequently contact their children to manage glucose levels, even when apart. There are few studies investigating how this control affects particularly adolescents and parents, and further research is of interest to increase the understanding of how to guide and support the families in the best way.

Healthcare – the diabetes team

The diabetes team can also follow the patient's glucose level via internet-based download systems, which enables more advanced advice at visits at the hospital and by telephone or digital visits. Most patients and parents probably experience this as helpful and positive, but it could also mean a negative effect for some who may experience

increased stress and feelings of inadequacy if they have difficulties understanding self-management advice and incorporating it into action.

Many adolescents with T1D and their parents report significant problems in communication with health-care providers, with a mismatch in perceived priorities [190], and difficulties getting the information they need to effectively manage their diabetes [191]. With the rapid development in technology during the last decade the members of the diabetes team must constantly stay informed about the new devices to be able to support patients and families. To improve communication and education from the diabetes team more research to explore the families' experiences of the support are needed.

Quality registers

A national quality register contains individualized data concerning patient problems, medical interventions, and outcomes after treatment within all health care production. They are integrated into clinical workflow and have the capacity to generate data in real time. In this way the different clinics receive continuous feedback of their own results and an opportunity to compare those with the results of other clinics and regions. In Sweden, there are around 150 national quality registers that provide the Swedish health care system with a unique opportunity to monitor quality and results. They also constitute valuable sources for research and innovation. Each register is supported by an organization of health care professionals and patient representatives, and they are responsible for developing the register together [192].

The National Diabetes Register (NDR) is a national quality register with the purpose to facilitate a systematical improvement of the health care for individuals with diabetes. The National Register for individuals with diabetes <18 years of age, Swediabkids, started in the year 2000 and was integrated into NDR in 2018. NDR offers an opportunity to compare diabetes health care in a local, regional, and national level [2].

The ethical concern in register-based research is the potential risk of violation of personal integrity when data is collected for one purpose and used for research without the individual's explicit consent. The participants are informed about the quality register before health care professionals start to report their data, but they do not have to sign an informed consent, and they can decide to opt out at any time. All the research based on data from national quality registers require an ethical approval from the Swedish Ethical Review Authority.

Objectives

The overall aim of this thesis is to explore which self-management methods give the best opportunity to achieve good glycaemic control in children and adolescents with T1D.

Specific aims:

Paper I: To a) investigate if the insulin method i.e., CSII compared to MDI can improve the glycaemic control in children and adolescents with T1D in Sweden and b) if there are any differences in BMI-SDS or incidence of severe events (hypoglycaemia or ketoacidosis) between the types of insulin administration.

Paper II: To a) investigate if CGM in combination with CSII compared to CGM in combination with MDI is better in achieving glycaemic control in children and adolescents and b) if there is any difference between isCGM and rtCGM in combination with the different insulin methods regarding HbA1c, incidence of severe events or BMI-SDS.

Paper III: To a) investigate if the insulin method i.e., CSII or MDI, can affect the incidence and duration of the partial remission period and b) what characterizes the partial remission period regarding sex, age at onset and incidence of severe events (hypoglycaemias and ketoacidosis).

Paper IV: To explore the patients' and parents' experiences of the new technology, the glucose target (HbA1c ≤48 mmol/mol), and the support from healthcare using qualitative methods.

Methods of analyses

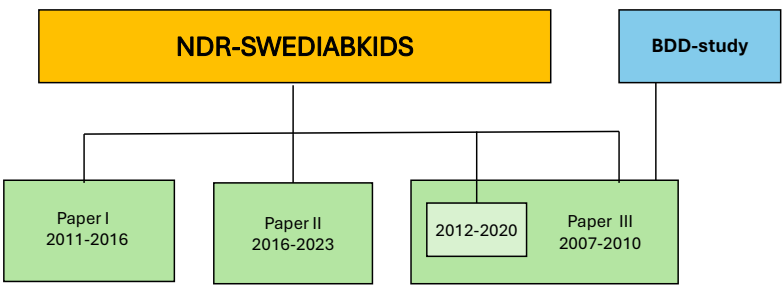
Schematic overview of methods

	I	II	III	IV
Study design	Prospective longitudinal observational study	Prospective longitudinal cohort study	Prospective longitudinal observational study	Qualitative study
Data sources	The Swedish National Quality Register (NDR-Swediabkids)	NDR-Swediabkids	NDR-Swediabkids and Better Diabetes Diagnosis study (BDD)	Paediatric diabetes clinic in Östersund hospital, Paediatric diabetes clinic in Umeå University hospital
Study population	35,624 patient years On average 6915 patients per year in 2011-2016	13,559 patients in 2016-2023 929 patients newly diagnosed T1D in 2016	3887 patients from NDR 3090 patients from BDD in 2007-2011 8182 patients (NDR) in 2012-2020	8 youths with T1D (15-17 years) with CSII and CGM 8 parents
Data collection	HbA1c, age, sex, date of diabetes onset, BMI-SDS, insulin method, severe hypoglycaemia, ketoacidosis	HbA1c, age, sex, date of diabetes onset, BMI-SDS, insulin method, CGM (is/rt), severe hypoglycaemia, ketoacidosis	HbA1c, age, sex, insulin method, total daily insulin dose, date of diabetes diagnosis, severe hypoglycaemia, ketoacidosis, C-peptide	Individual interviews
Statistical analyses Comparison	Independent t-test, one-way ANOVA, multiple logistic regression, multivariable linear regression	Multivariable linear regression, independent t-test, Chi2-test, one-way ANOVA	Independent two-sample t-test, Mann-Whitney U-test, generalized linear mixed regression	Qualitative content analysis
Outcome	HbA1c Incidence of severe hypoglycaemias	HbA1c Incidence of severe hypoglycaemias, ketoacidosis	Partial clinical remission (IDAA1c), C-peptide	Experiences of technology, the glucose target and support from healthcare

Abbreviations: T1D, type 1 diabetes; CSII, continuous subcutaneous insulin infusion; CGM, continuous glucose monitoring; BMI-SDS, body mass index (kg/m^2) standard deviation scores; is, intermittent scanning; rt, real time; IDAA1c, insulin dose adjusted hemoglobin A1c

In this thesis, both quantitative and qualitative methods have been used. The project utilizes data from the Swedish National Diabetes Register (NDR-Swediabkids) and the Better Diabetes Diagnosis Register (BDD). Three of the studies were prospective, longitudinal, observational studies with data from the NDR-Swediabkids, where one includes a cross-sectional comparison (Paper I), and one is cross-linked with the BDD-register (Paper III). One study was an interview study with qualitative content analysis (Paper IV).

Figure 3. Flowchart over the registers in the thesis in study I-III



The study population in papers I-III consists of all children and adolescents from 0 to 17 years of age with T1D, as reported to the Swedish National Diabetes Register for Paediatric Diabetes in Sweden, NDR-Swediabkids, that started in the year 2000. All 43 paediatric clinics in Sweden have used Swediabkids since 2007, resulting in a coverage of nearly 98% for prevalent cases [2]. Since 2008, Swediabkids has been web-based and clinical data are recorded prospectively from every patient visit to the out-patient paediatric clinics, which is usually three to four times yearly per patient. The register is repeatedly validated against the Swedish Prescribed Drug Register for incident cases. The Prescribed Drug Register is maintained by the National Board of Health and Welfare and covers all redeemed medical prescriptions since July 2005 [193]. In 2016, data from 7,310 unique patients up to 17 years of age were recorded in Swediabkids from 27,186 visits, and on average 6,915 patients per year were recorded from 2011 to 2016. There were on average 806 patients per year recorded with newly diagnosed T1D from 2007-2011, and in 2012-2023, on average, 922 patients per year were recorded [2]. In 2018, Swediabkids was integrated into the Swedish National Diabetes Register (NDR), with patients with diabetes >18 years of age, and is now referred to as NDR-Swediabkids. At every visit to the out-patient paediatric clinic, anthropometrical data (weight and height), HbA1c, insulin method, total daily insulin dose and incidences of severe hypoglycaemia

or ketoacidosis are registered. Since 2016 data on usage of isCGM or rtCGM are registered.

The Better Diabetes Diagnosis (BDD) is a prospective, on-going national study that started in 2005 in Sweden to classify the type of diabetes in all newly diagnosed children and adolescents 0 to 17 years of age. This ongoing study is based on patients from all 43 paediatric clinics in Sweden. Blood samples from patients with newly diagnosed diabetes are collected and analysed for autoantibodies, HLA genotype and levels of C-peptide. In 2006, approximately 75% of all children and adolescents with newly diagnosed diabetes in Sweden were registered in the study, and today the coverage is over 95% [122]. C-peptide was analysed at onset of diabetes and after one year in the study during 2005 to 2010. Informed consent was obtained from the participants and their parents/caregivers in the study. In total, during the period 2007 to 2010 there were 1,148 patients having C-peptide values registered at their diagnosis of diabetes and after one year. Since 2011, analyses of HLA profile, autoantibodies, and C-peptide levels are part of clinical routine in Sweden for all paediatric patients with suspected diagnosis of diabetes.

Data measurements

HbA1c

HbA1c, also known as glycated haemoglobin, is a blood test that provides an average measure of blood glucose levels over the past 2-3 months [77].
At the different hospitals using the NDR-Swediabkids, analyses of HbA1c were performed according to different laboratory methods but all are quality-assured through Equalis (External Quality Assurance in Laboratory Medicine in Sweden), which makes it possible to compare HbA1c values across different clinics [194]. HbA1c is presented as International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol) and National Glycohemoglobin Standardization Program (NGSP) units (%). The conversion of HbA1c from IFCC (mmol/mol) to NGSP (%) was done using the tool provided by the National Glycohemoglobin Standardization program [195].

Severe events

Severe hypoglycaemia is defined as blood glucose <3.9 mmol/L together with an event involving unconsciousness and/or seizure, and ketoacidosis (when the body in lack of insulin begins to break down fat as fuel and via the liver produces ketones causing acidosis in the blood), defined as pH<7.3 with the number of events since previous visit to the out-patient clinic. Diabetic ketoacidosis (DKA) is only reported to the NDR-Swediabkids when pH<7.3.

BMI-SDS

Anthropometrical data (weight and height) were collected at each clinical visit. Body Mass Index (BMI) standard deviation scores (BMI-SDS) were calculated at each visit using the BMI reference values for Swedish children [128].

C-peptide

Serum C-peptide was analysed from random non-fasting blood samples collected before the first insulin dose was administered at diagnosis of diabetes and from a non-fasting sample collected at random 1 year later. They were measured at Linköping University, Sweden, with a time-resolved fluoroimmunoassay (AutoDELFIA™ C-peptide kit, Wallac, Turku, Finland), with a detection level of 0.03 nmol/L. Each assay was validated by inclusion of a C-peptide control module containing a high, a medium, and a low-level control (Immulite, DPC, UK). A 1224 MultiCalc® program (Wallac) was used to calculate the levels of C-peptide.

Study designs

Paper I
This was a register study with longitudinal data from 2011 to 2016 extracted from NDR-Swediabkids with both cross-sectional (6 years) and longitudinal (4 years) comparisons. Main end points were changes in HbA1c, BMI-SDS, and incidence of severe hypoglycaemia. The period 2011-2016 was selected because of the general decrease in mean HbA1c that occurred during these years while the frequency of CSII usage increased. The study was approved by the Regional Ethics Committee at Umeå University, Umeå, 2017/12-31.

Paper II
A register study with longitudinal data from NDR-Swediabkids. Data were extracted from the period 2015-01-01 to 2023-12-31, but since isCGM was not approved for children before 2015 the registration on presence of is/rtCGM started in 2016 (retroactive from 2015), and due to very low coverage on CGM data in 2015 we excluded that year. Main end points were changes in HbA1c, BMI-SDS, and incidences of severe hypoglycaemia or ketoacidosis. The study was approved by the Swedish Ethical Review Authority, 2019-00116 and 2024-01-30.

Paper III
A register study with longitudinal data from NDR-Swediabkids and the Better Diabetes Diagnosis study (BDD). The period 2007-2010 was selected since the BDD study had analysed C-peptide at onset of T1D and after one year during these years. We compared the definition for partial remission used in Sweden during this time [121]: Total Daily Dose of Insulin (TDDI) <0.5 U/kg/day + HbA1c <57 mmol/mol with the Insulin Dose Adjusted A1c (IDAA1c) definition: HbA1c (%) + [4 x total daily dose of insulin (U/kg/day)] ≤9. The study was approved by the Regional Ethics Committee in Stockholm, 2014/2011-31 and by the Swedish Ethical Review Authority 2020-05894.

Paper IV
A qualitative method with an inductive approach was chosen since we wanted to gain deeper insight into participants' personal experiences and to analyse their narratives in an open way searching for patterns. Focused open individual interviews were performed according to Tjora [196] and Bryman [197], and the results were analysed using qualitative content analysis according to Graneheim and Lundman [198].

Subjects

A strategic selection of 8 youths (15-17 years) with T1D, insulin pump and CGM, and with diabetes duration >8 years and having experienced the old glucose target HbA1c <52 mmol/mol. The diabetes nurses at the paediatric diabetes clinic at Östersund hospital and at Umeå University hospital asked the youths that fulfilled the inclusion criteria's, during routine clinical visits, if they were interested in participating in the study. There were 4 participants with poor glucose metabolic control (HbA1c > 64 mmol/mol) and 4 participants that achieved the glucose target HbA1c ≤48 mmol/mol. Five youths had their out-patient visits at the paediatric clinic at Östersund hospital (2 girls and 3 boys),

and three at the Umeå University hospital (2 girls and 1 boy). Eight parents participated, three (2 mothers and 1 father) from Umeå, and five (2 mothers and 3 fathers) from Östersund. One patient declined participation due to not being willing to talk about diabetes, while one of the parents participated, nonetheless. The participants had to be able to speak and understand Swedish without problem, and having previous/currently contact with the researchers doing the study was an exclusion criterion.

Location

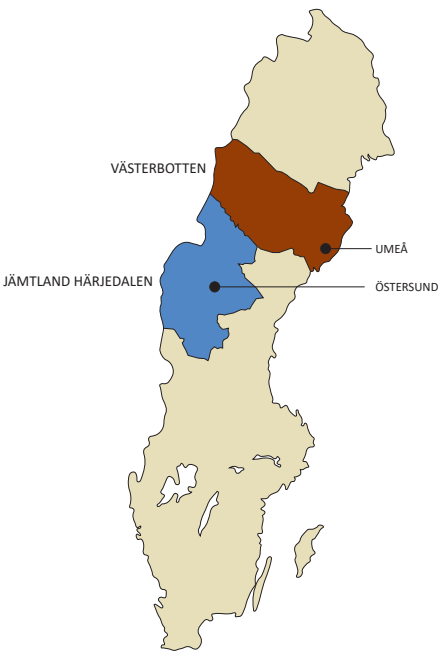


Figure 4. Map of Sweden with study sites highlighted.

The Region Jämtland Härjedalen has a population of approximately 130,000 inhabitants [199], and it is sparsely populated with long distances between villages. There is only one hospital in this Region located in the city Östersund, where outpatient and hospital care for all children and adolescents with diabetes is provided. The county Östersund has a population of 65,000 inhabitants (14,500 below the age of 19) [200]. At the end of the year 2024 the number of children and adolescents with diabetes receiving care at the paediatric diabetes unit at Östersund hospital was 100 [2].

The Region Västerbotten has a population of approximately 280,000 inhabitants, and there is one University hospital in Umeå and one hospital in Skellefteå, where outpatient

and hospital care for children and adolescents with diabetes is provided. The county Umeå has a population of 133,000 inhabitants (27,600 below the age of 19) [201]. At the end of the year 2024, the number of children and adolescents (0-17 years) with diabetes receiving care at the paediatric diabetes unit at Umeå University hospital was 250 [2].

All patients included in the study had T1D with a clinical history of typical diabetes symptoms at onset, and all of them required insulin treatment from the date of diagnosis of diabetes.

Data collection

Data were collected through individual interviews in Swedish, conducted face-to-face or online, depending on the participants preference. Due to geographical distance, in-person interviews were not possible with the participants from Umeå, and all six interviews were conducted online. Four of the interviews in Östersund were conducted online and six interviews were conducted face-to-face in a room at the paediatric clinic at Östersund hospital. An interview guide to maintain structure with open-ended and follow-up questions to both youth and parents was used. The interviews were recorded digitally (Olympus VN-541PC), by the first author, there was no time restriction, and the participants were asked at the end whether they had additional comments.

Ethical consideration

Ethical approval for the study was obtained from the Swedish Ethical Review Authority, Dnr 2023-00817-01. The participants received oral and written information about the study when they were asked to participate. Information was given that it was voluntary, that all collected data would be kept safe and that it will not be possible for any information to be linked to any person. All participants gave signed informed consent before inclusion, with both parents of the participating youth providing consent. Data were securely stored in computer files protected by two-factor authentication, and physical transcripts were kept in a locked cabinet.

Quantitative data analyses

Statistical methods

All statistical analyses were performed using IBM SPSS version 24 (Paper I), version 27 (Paper III), and version 29 (Paper II). The data distribution was examined for all variables using histograms and descriptive statistics. The level of statistical significance was set at $p<0.05$.

Paper I
The annual data was stratified according to insulin method (CSII vs. MDI), sex, age groups (0-6, 7-12, 13-17 years), and HbA1c groups (<48, 48-55.9, 56-63.9, 64-71.9, and >72 mmol/mol). The longitudinal data were stratified according to insulin method (CSII vs. MDI) and sex. Independent two-sample t-test was used for normally distributed data, and one-way ANOVA for calculating p-trends over time. The association between insulin pump and HbA1c, BMI-SDS, diabetes duration, and sex was analysed with multiple logistic regression, calculating OR with 95% confidence interval (CI). The analyses were adjusted for HbA1c, BMI-SDS, duration of diabetes, and sex (male reference). Multivariable linear regressions with two models were performed for a) HbA1c adjusted for sex, BMI-SDS, and duration of diabetes and b) BMI-SDS adjusted for HbA1c, sex, and duration of diabetes. A linear mixed model was used to study HbA1c, BMI-SDS, and severe hypoglycaemic events of the cohort to adjust for the different number of patients at different times.

Paper II
The annual data was stratified according to insulin method (CSII vs. MDI), CGM (is/rt) or non-CGM, sex, age groups (0-6, 7-12, 13-17 years), and duration groups (<5, 5-10, >10 years). In the cohort 2016 with newly diagnosed T1D, HbA1c values taken 5-7 months after diagnosis was selected to decrease the risk of patients being in partial remission. A multivariable linear regression with two models, one where the dependent variable was HbA1c, and the independent variables were sex, CGM, insulin method (CSII), age at diagnosis and the other model where the dependent variable was BMI-SDS. Both mean HbA1c and mean BMI-SDS during the time period 2016-2023 and the last HbA1c and BMI-SDS values in 2023 were used in the models. All descriptive statistical analyses were performed with independent two-sample t-test for normally distributed data, Chi2-test, and one-way ANOVA for comparison of multiple groups.

Paper III
The annual data were stratified according to the insulin delivery method (CSII vs. MDI), sex, partial remission status (IDAA1c ≤9 vs. IDAA1c >9) or according to the Swedish, clinical remission definition, age at diagnosis group (0-6, 7-12, 13-17 years old), and duration group (0-3, 3-12, 12-24 months after diabetes diagnosis). We stratified the groups being in partial remission at 3 months, after 1 year, and still in partial remission after 2 years. For normally distributed data, differences between groups were tested with independent two-sample t-tests. A non-parametric Mann-Whitney U test was used to compare the skewed data on C-peptide between groups. The interquartile range (IQR) was calculated by subtracting the 75^{th} and 25^{th} percentile of the median. A generalized linear mixed regression model was performed to account for repeated measurements, and the outcome was being in remission at each time point.

Qualitative data analyses

Paper IV
The interviews were transcribed verbatim by two medical secretaries working at the paediatric department at Östersund hospital, and the transcripts were de-identified for

confidentiality. Qualitative content analysis according to Graneheim and Lundman [198,202,203] was used to analyse the data, and this method emphasizes the identification of variations through similarities and differences within the material. The analysis started with repeated readings of the transcripts to gain a comprehensive understanding of the content. Meaning units were identified and condensed to retain essential content while reducing length. These condensed units were then labelled with codes to capture their essence. Codes were then grouped and abstracted into categories and subcategories by their commonalities at a manifest level. No further abstraction was performed. Co-creation in the analysis is often described as consensus, and to ensure dependability both the first and last author read the material independently, identified meaning units and coded the material. To further ensure dependability, the final material was reviewed by the whole research team, who after discussions agreed on categories and subcategories. All steps of the analysis were conducted manually. We have strived to achieve trustworthiness (credibility, dependability, confirmability, and transferability) by describing the analytical process in detail, providing quotations from the interviews, involving several researchers in the analyses, and describing the sample and context in as much detail as possible.

Results

Paper I, Comparing CSII – MDI

In total 35,624 patient years (54% boys) of patients from 0 to 17 years of age were available (Table 1).

Table 1. Baseline characteristics from the years 2011-2016 presented as mean (95% CI) for HbA1c and BMI-SDS

	2011	2012	2013	2014	2015	2016	p-trend
0-6 years							
n	808	832	827	829	864	865	
Female, n (%)	384 (47.5)	412 (49.5)	400 (48.4)	391 (47.2)	403 (46.6)	401 (46.4)	
MDI (%)	51.1	44.4	39.2	31.9	26.0	21.3	<0.001
CSII (%)	39.9	44.7	50.7	57.0	62.3	67.8	<0.001
HbA1c (mmol/mol (CI))	55.7(55.0-56.3)	55.2(54.5-55.9)	52.8(52.2-53.4)	52.8(52.3-53.4)	53.4(52.9-54.0)	53.2(52.7-53.7)	<0.001
BMI (SDS (CI))	0.49(0.41-0.56)	0.49(0.41-0.57)	0.49(0.42-0.56)	0.53(0.46-0.60)	0.52(0.45-0.59)	0.58(0.51-0.65)	NS
7-12 years							
n	2403	2449	2506	2561	2582	2667	
Female, n (%)	1137 (47.3)	1160 (47.4)	1185 (47.3)	1247 (48.7)	1287 (49.8)	1292 (48.4)	
MDI (%)	56.3	51.8	48.9	46.0	39.3	35.8	<0.001
CSII (%)	34.7	38.9	41.7	44.9	50.1	55.7	<0.001
HbA1c (mmol/mol (CI)	60.3(59.9-60.7)	58.9(58.5-59.3)	56.4(56.0-56.8)	55.0(54.6-55.4)	55.2(54.9-55.6)	55.2(54.9-55.6)	<0.001
BMI (SDS (CI))	0.58(0.54-0.62)	0.58(0.54-0.62)	0.57(0.53-0.61)	0.56(0.52-0.60)	0.57(0.53-0.61)	0.61(0.56-0.65)	NS
13-17 years							
n	3570	3551	3493	3542	3673	3769	
Female, n (%)	1660 (46.5)	1630 (45.9)	1594 (45.6)	1618 (45.7)	1673 (45.5)	1720 (45.6)	
MDI (%)	60.0	56.9	55.1	52.4	48.8	45.4	<0.001
CSII (%)	33.7	37.4	38.9	40.6	44.5	48.2	<0.001
HbA1c (mmol/mol)	65.4(64.9-65.9)	64.9(64.5-65.4)	63.2(62.7-63.7)	61.3(60.8-61.8)	60.4(60.0-60.8)	59.8(59.4-60.2)	<0.001
BMI (SDS (CI))	0.66(0.63-0.70)	0.66(0.63-0.70)	0.70(0.67-0.74)	0.70(0.66-0.73)	0.71(0.67-0.75)	0.71(0.67-0.74)	NS

The frequency of CSII treatment increased between 2011 and 2016 from 35% to 56% in boys and 41% to 60% in girls (p_{trend} for both <0.001).
Overall, we found that the use of CSII was associated with female sex, higher BMI-SDS, and longer duration of diabetes. In 2011, the likelihood of CSII was 30% higher in girls compared to boys (OR 1.30 [CI 1.16-1.45], p=0.001), which decreased to 22% by 2016 (OR 1.22 [CI 1.10-1.36], p=0.001). There was an association between a high HbA1c and higher BMI-SDS, female sex, and long diabetes duration. A high BMI-SDS was associated with CSII treatment, higher HbA1c and female sex. HbA1c was approximately 0.7-1.5 mmol/mol lower with CSII treatment compared to MDI treatment.

Patients using CSII were generally younger but had a longer diabetes duration compared to those treated with MDI, except for the HbA1c group >64 mmol/mol.

There was an overall decrease in HbA1c of around 2-5 mmol/mol in all the different age and sex groups. There was no difference in mean HbA1c between the patients using CSII or MDI except for the group with HbA1c >72 mmol/mol; 2015 (CSII: 77.4 mmol/mol vs. MDI: 79.8 mmol/mol, p<0.01) and in boys 13-17 years; 2016 (CSII: 60.3 mmol/mol vs. MDI: 58.2 mmol/mol, p<0.001).

Longitudinally there was no difference in the BMI-SDS or in the number of severe hypoglycaemic events, but there was an age-dependent increase in mean HbA1c similar for both insulin methods.

More girls (54%) than boys changed their insulin delivery method, and most changes were from MDI to CSII treatment. The mean age (11 years) was the same and there was no difference in the BMI-SDS or in the number of severe hypoglycaemic events between those changing and not changing insulin delivery method. The mean HbA1c for those who changed insulin delivery method increased for every year like the group not changing method.

Paper II, Comparing CGM and insulin delivery methods

Data from 13,559 patients (55% boys) (0-17 years) were available from 2016-2023 (Table 2).

Table 2. Baseline characteristics of the CGM and Non-CGM group presented as mean (SD) for HbA1c and BMII

	CGM			Non-CGM		
	MDI	CSII	p	MDI	CSII	p
Patients n (%)	3249 (24.0)	8689 (64.1)	0.011	996 (7.3)	625 (4.6)	NS
Boys n (%)	1908 (25.7)	4646 (62.5)		583 (7.8)	301 (4.0)	
Girls n (%)	1341 (21.9)	4043 (66.1)		413 (6.7)	324 (5.3)	
Age (years) n (%)			<0.001			NS
Mean/SD	10.4/4.3	6.4/4.1	<0.001	10.4/4.4	8.0/4.0	<0.001
0-6	738 (13.6)	4202 (77.4)		235 (4.3)	256 (4.7)	
7-12	1427 (25.0)	3619 (63.3)		403 (7.0)	266 (4.7)	
13-17	1082 (44.9)	867 (36.0)		358 (14.8)	103 (4.3)	
HbA1c mmol/mol (SD)*	61.0/21.2	59.4/18.0	<0.001	64.3/21.5	61.2/16.8	0.003
BMI-SDS (SD)	0.52/1.19	0.48/1.15	NS	0.47/1.32	0.64/1.21	0.014
Hypoglycaemia n (%)	232 (7.1)	861 (9.9)	0.001	43 (4.3)	30 (4.8)	0.002
Ketoacidosis n (%)	95 (2.9)	375 (4.3)	0.012	24 (2.4)	14 (2.2)	NS
Duration (years) n (%)			0.013			0.030
Mean/SD	4.8/4.4	7.3/3.9	<0.001	5.2/4.5	7.3/4.4.	<0.001
<5	1824 (30.8)	3386 (57.3)		512 (8.7)	191(3.2)	
5-10	978 (18.7)	3656 (69.8)		329 (6.3)	272 (5.2)	
>10	447 (18.6)	1647 (68.3)		155 (6.4)	162 (6.7)	

*HbA1c from 2016

The frequency of CGM increased between 2016 to 2023 from 79% to 99%, and the frequency of insulin pump treatment increased from 64% to 74%. Patients with CGM and insulin pump were younger or had longer diabetes duration.

Over the years 2016-2023, patients with CGM and insulin pump had lower mean HbA1c compared to the group with CGM and MDI treatment, 59.4 mmol/mol vs. 61.0 mmol/mol, p<0.001. Those without CGM having insulin pump had a lower mean HbA1c compared to the group without CGM treated with MDI, 61.2 mmol/mol vs. 64.3 mmol/mol, p=0.003. Patients without CGM treated with insulin pump had a higher BMI-SDS compared to the group without CGM and MDI treatment, 0.64 vs. 0.47, p=0.014.

The prevalence of severe events, i.e., both hypoglycaemia and ketoacidosis, was higher in the group with CGM and insulin pump compared to those with CGM and MDI treatment, 9.9% vs. 7.1%, p=0.001 and 4.3% vs. 2.9%, p=0.012, respectively.

Longitudinal data from 2016-2023 with newly diagnosed T1D, demonstrated more patients with CGM in the youngest age group (0-6 years) compared to the oldest age group (13-17 years) 56.0% vs. 39.1%, p<0.001 (Table 3).

Table 3. Baseline of characteristics of newly diagnosed T1D 2016, presented as mean (SD) for HbA1c and BMI-SDS

	CGM	Non-CGM	p
Patients n (%)	407 (45.3)	492 (54.7)	
Boys n (%)	250 (46.0)	293 (54.0)	NS
Girls n (%)	157 (44.1)	199 (55.9)	NS
Age groups years n (%)			<0.001
0-6	134 (56.0)	105 (44.0)	
7-12	178 (42.7)	239 (57.3)	
13-17	95 (39.1)	148 (60.9)	
HbA1c mmol/mol (SD)	58.1 (18.4)	69.3 (25.7)	<0.001
BMI-SDS (SD)	0.36 (1.1)	0.29 (1.3)	NS
Hypoglycemias n (%)	43 (4.8)	47 (5.2)	NS
Ketoacidosis n (%)	22 (2.4)	29 (3.2)	NS
Insulin method MDI n (%)	296 (41.5)	418 (58.5)	NS
Insulin method CSII n (%)	111 (60.0)	74 (40.0)	NS

Mean HbA1c was lower in the CGM group compared to the group without CGM, 58.1 mmol/mol (18.4) vs. 69.3 mmol/mol (25.7), p<0.001. There were no differences in BMI-SDS, severe events with hypoglycaemia or ketoacidosis between the CGM or Non-CGM group.
Patients with CGM and insulin pump had lower mean HbA1c compared to the group with CGM and MDI treatment, 51.6 mmol/mol vs. 60.5 mmol/mol, p=0.005.
Those with MDI treatment without CGM had a higher mean HbA1c and more events with ketoacidosis compared to those without CGM treated with insulin pump, 70.9 mmol/mol vs. 52.6 mmol/mol, p=0.036 and 4.5% vs. 1.4%, p=0.049, respectively.

Patients with rtCGM were younger, had longer diabetes duration and used insulin pump to a larger extent. Those with rtCGM and insulin pump had lower mean HbA1c compared to treatment with rtCGM and MDI, (2016); 59.4 mmol/mol vs. 61.0 mmol/mol, p<0.001 with a further decrease in 2023 to 53.3 mmol/mol vs. 54.9 mmol/mol, p<0.001.
The group with isCGM had higher mean HbA1c values compared to the rtCGM group regardless of insulin method. However, the combination of CGM and MDI resulted in the relatively largest reduction in mean HbA1c compared to treatment with insulin pump with or without CGM or MDI treatment without CGM.
We found that a high HbA1c was associated with female sex, non-usage of CGM, and MDI treatment and a high BMI-SDS was associated with female sex and young age at diabetes diagnosis. There was no interaction effect between CGM and insulin method for neither mean HbA1c nor BMI-SDS.

Paper III, Partial clinical remission

In total, data from 3887 patients (56% boys) from 0 to 17 years of age were available (Table 4).

Table 4. Baseline characteristics for new-onset T1D presented as mean (SD) for HbA1c and BMI-SDS

	2007	2008	2009	2010	2011
Patients total, n (%)	779 (100)	722 (100)	805 (100)	784 (100)	797 (100)
Male, n (%)	429 (55)	419 (58)	458 (57)	436 (55.5)	426 (53.5)
Female, n(%)	350 (45)	303 (42)	347 (43)	348 (44.5)	371 (46.5)
Age (years) mean (SD)	10.1 (1.2)	9.5 (4.6)	9.5 (4.6)	9.6 (4.6)	9.4 (4.6)
HbA1c (mmol/mol) mean (SD)	65.4 (23.3)	61.1 (19.0)	62.6 (19.6)	63.6 (19.8)	63.8 (21.3)
BMI-SDS, mean (SD)	0.32 (1.2)	0.46 (1.1)	0.38 (1.2)	0.40 (1.2)	0.33 (1.2)
Partial remission IDAA1c (%)					
3 months	44.7	49.7	45.2	47.9	50.8
12 months	29.9	35.0	31.6	32.1	38.7
24 months	20.6	26.6	25.1	26.5	35.2

There were more patients with partial remission using the IDAA1c definition compared with the Swedish clinical definition, at 3 months (48% vs. 36%), at 12 months (33% vs. 14%), and at 24 months (26% vs. 5%). There was an increase in the frequency of partial remission using the IDAA1c definition between 2007-2011 and 2012 -2020 of approximately 5%.

Boys had an increased likelihood of partial remission compared with girls: 20% at 3 months (OR: 1.2, 95% CI: 1.00-1.43), 23% at 12 months (OR: 1.23, 95% CI: 1.04-1.46), and 25% at 24 months (OR: 1.25, 95% CI: 1.05-1.50).

Fewer children in the youngest age-group (0-6 years) were in partial remission at 3 and 12 months but not at 24 months from onset compared with the older age-groups.

Partial remission was associated with CSII treatment throughout follow-up and subgroup analysis for the group being in partial remission having data from 3, 12, and 24 months indicated that CSII treatment at 3 months increased the probability of reaching partial remission and maintaining it for 24 months (OR: 3.26, 95% CI: 1.10-9.69).

There were fewer incidents with severe hypoglycaemia and ketoacidosis among those with partial remission at 12 and 24 months, $p<0.05$.

Median serum C-peptide at diagnosis was higher in the group that later entered partial remission (0.25 nmol/L vs. 0.22 nmol/L), $p<0.001$, as well as after 1 year (0.26 nmol/L vs. 0.22 nmol/L), $p<0.001$, and mean HbA1c was lower after 2 years (50.4 mmol/mol vs. 59.0 mmol/mol), $p<0.001$. There was no distinct level of C-peptide at diagnosis that could predict later partial remission due to a large overlap.

Paper IV, Patients and parents' experiences of the new technology

The analysis resulted in three categories, and nine subcategories (Table 5).

Table 5. An overview of the analysis with the categories and subcategories

Categories	Subcategories
To live with insulinpump and CGM as a youth with T1D	*Strengthened independence and increased freedom*
	Improved ability to control and easier to maintain stable glucose levels
	Importance of parental support
Parental engagement in their youths diabetes	*Increased freedom with reduced need of support*
	Improved night sleep, ability to relaxation and impact on the psychological health
	Easier to keep control of glucose balance with trust in technology
Professional support from the diabetes team	*Good support for both youth and their parents*
	Positive experience of technical support
	The importance of gluco-metabolic measurements

Overall youths with T1D and their parents expressed the increased independence and freedom that it has implied. They emphasized feeling more satisfied and secure with increased control, but the youths emphasized the need for continued support from their parents and the parents emphasized that they still wanted to be involved together with the diabetes team. This leads to a conflict concerning the need for the youths to separate from the parents while emerging into adulthood and for the healthcare support to facilitate transition to adult care.

New technology of insulin pumps and CGM facilitates everyday life for both youths with type 1 diabetes and their parents. It challenges the diabetes teams to support the families when they have problems with the technology and highlights the need for the team members to constantly keep up with the rapid technical development. It emphasizes the importance of supporting parents during the transition process to enable their youths to take over responsibility for their diabetes and maintaining the glucose target as young adults.

Surveillance with alarm functions and improved glycaemic control leads to better sleep at night for the parents and reduces stress in the family. The opportunity for the parents to follow their youth's glucose values does not seem to be a problem to the youths who instead experience a feeling of increased security.

The lowering of the glucose target in 2017 is not anything that neither youth nor parents have had much concern about, and they consider the gluco-metabolic measurement Time in tight range to be more useful in everyday life.

Discussion

The main result of this thesis is that technical devices, i.e., insulin pump and CGM, can improve glycaemic control without any increase in severe hypoglycaemia. However, there is an association between CSII treatment and increased BMI-SDS, especially in teenage girls, which may lead to overweight and obesity.
CSII treatment seems to contribute to a longer partial remission period which can reduce glycaemic variability and decrease the risk of long-term complications.
There is a need for patients and parents to receive advanced technical support in how to use the technology from the healthcare diabetes team as well as support during the important transition process.

Insulin delivery method

In study I, we found a minute decrease in HbA1c in CSII treated patients. Overall, there was a general, larger reduction in mean HbA1c over time irrespective of treatment without any increase in severe hypoglycaemia. During the last 15 years the use of CSII therapy has increased by more than 50% in Sweden, and today around 80% of children and adolescents with T1D are using CSII therapy [2].

The difference in HbA1c between CSII and MDI treatment groups was only 0.7-1.5 mmol/mol, and this is likely of little clinical relevance. The usage of CSII varies between different counties and paediatric clinics but there is no correlation between the clinics mean HbA1c and frequency of CSII usage. Even though some paediatric clinics today have a large proportion of automated insulin delivery pumps (AID), they do not achieve a lower mean HbA1c compared to clinics with less use of the latest hybrid closed-loop technology [6]. This indicates that self-management of T1D is a complex process and that the members of the diabetes team have an important role in education and support since technical device is not the sole solution.

Previous meta-analysis of randomised controlled studies of paediatric cohorts using CSII have shown a modest HbA1c reduction [204], but most of these studies had a duration less than 3 months. Our study is based on real-life data which might explain the different results compared to the RCTs. Our findings corroborate some previous studies [50,51,205] which demonstrated no difference in glycaemic control between CSII and MDI, but contradicts a study [206], with data from the National Diabetes Registry in Denmark (DanDiabKids), where they followed patients for more than 5 years and showed that patients in all age groups achieved an improved metabolic control on CSII treatment. However, in their study there was many patients (50%) that changed insulin delivery method from MDI to CSII treatment, which could have affected the result. In Denmark, the registry collects data on a yearly basis and HbA1c is analysed centrally in one specialized laboratory for diabetic children eliminating the possibility of inter-centre variability which affects validity.

Possible explanations to our findings compared to other studies could be different indications for CSII treatment and different approaches to education in the multidisciplinary teams, which can lead to different education of patients and families. There is no standardized curriculum in Sweden for how to start CSII treatment in a patient, so this procedure varies between different paediatric clinics. Education and training of patients and families starting CSII and/or CGM treatment is more time consuming than traditional MDI therapy and could be influenced by staffing and resources in different diabetes clinics [207]. While some diabetes teams take care of all education themselves, others receive help from the companies manufacturing the technical devices. This could mean that interest in technology, knowledge, and ability to educate patients and families differs between different diabetes teams in the country. In contrast to many other countries in the world, the costs for insulin pumps in Sweden are covered by the National Healthcare system eliminating the cost for the patients and their families. This is positive in the aspect of equality, but in 2019, Grip et al demonstrated in a health economic national real-world study with data from NDR with patients with T1D >18 years of age (2005-2013), that insulin pump therapy showed additional costs compared to MDI [208]. However, they emphasized that the time frame may need to be longer to detect differences in treatment effects that have consequences for total costs exceeding those in the study.

We also found a higher BMI-SDS in teenage girls using CSII treatment, and this is consistent with the findings of other studies from the Nordic countries [209,210] as well as from the rest of the world demonstrated in the SWEET project [71]. One explanation could be that girls with a high BMI-SDS might have an insulin resistance, which can lead to a higher HbA1c, and they will be provided with CSII treatment to improve their glycaemic control. Other studies have also shown that children and adolescents with T1D using intensive insulin regimens have increased BMI compared to those with less intense therapy (≤3 injections per day) [47,211]. The intensified insulin treatment via CSII might cause a need of extra carbohydrates due to hypoglycaemic events and use of more insulin due to frequent meals [210]. In study II, we could confirm that treatment with CSII was associated with a higher BMI-SDS regardless prevalence of CGM. It is possible that a more flexible lifestyle with an insulin pump might increase the energy intake, resulting in a positive energy balance.

The DCCT (Diabetes Control and Complications Trial) showed that patients using intensive insulin therapy had a reduced incidence and progression of micro- and macrovascular complications and lower incidence of major cardiovascular events [152]. However, at the same time there was an association between intensive insulin treatment and a higher incidence of excess weight gain, central obesity, insulin resistance, dyslipidaemia, and elevated blood pressure [149]. However, recent studies indicate that AID systems improve glycaemic control without increasing BMI-SDS which is promising for the future [212,213].

Samuelsson et al [41] showed that teenage girls with T1D have an increased risk of complications in adulthood, which emphasizes the importance of helping this group to achieve a better glycaemic control without negatively affecting other aspects of their

health, such as increasing the risk of obesity. The multidisciplinary diabetes teams have an important role not only in supporting patients and families with technical advice concerning devices, but also with healthy lifestyle choices without increasing the burden of the disease.

There is now evidence that insulin pumps have impact on the metabolic control and comparisons of large diabetes registries with nearly 55,000 children and adolescents with T1D showed that pump use was associated with lower mean HbA1c (CSII 64 ±14 mmol/mol vs. MDI 69 ±17 mmol/mol, p<0.001) [214]. An international network of reference centres, the SWEET registry, reported that pump use was associated with lower HbA1c and daily insulin dose compared to MDI [5].

Meta-analyses have shown decreased rates of severe hypoglycaemia [215], reductions in mean HbA1c [204,215,216], and a reduction of total daily insulin doses with insulin pump therapy in adults and adolescents [204,216]. It has also been reported in young children that CSII reduces the incidence of severe hypoglycaemic events which is an important feature of its use in this age group [44-46].

Zimmermann et al (2025) demonstrated analysis of longitudinal data from several paediatric diabetes registries with more than 100,000 participants and showed that between 2013 and 2022 glycaemic outcomes have improved parallel to increased use of diabetes technology [217]. The highest proportions of CSII use were reported in DanDiabKids (Denmark), NCDR (Czech republic), and Swediabkids and since these three registries were in the top four for achieving target glycaemic outcomes, it has been suggested that CSII might be a major factor for reaching glycaemic targets [217].

Furthermore, the incidence of microvascular complications was investigated in an Australian study, comparing CSII and MDI including nearly 1,000 patients (12-20 years) with a diabetes duration of more than five years. There was no difference in HbA1c between patients treated with CSII (70 mmol/mol) and MDI (72 mmol/mol) (p=0.7). However, CSII treatment was associated with a lower risk of retinopathy (OR 0.66, 95% CI 0.45-0.95, p=0.029) and peripheral neuropathy (OR 0.63, 95% CI 0.42-0.95, p=0.026) [218]. It is possible that this finding could be due to an increased glucose variability with MDI treatment compared to CSII which might contribute to more stable glucose levels. This is emphasized by the latest technology with AID systems increasing Time in target and reducing the glucose variability (SD).

According to ISPAD Guidelines 2024 insulin pump therapy is recommended and appropriate for youth with diabetes, regardless of age, baseline glycaemia, and T1D duration [219]. AID systems are strongly recommended for youth to improve Time in range by minimizing hypo- and hyperglycaemia and reduce burden of care [219]. Regarding sustainability the increased use of insulin pumps and CGM leads to a decreased use of insulin pens and blood sugar test sticks which is positive for the environment.

Glucose monitoring

In the last decade the frequency of CGM use has increased from 45% to 99% and there has been a constant improvement in the technology leading to smaller and more user-friendly sensors without requirements of calibrations with capillary blood glucose finger pricks [6]. This technical evolution has facilitated everyday life for children and adolescents with T1D and their parents.

In study II we found that mean HbA1c in the group using CGM was lower than in the group without CGM, but there was no difference in BMI-SDS or incidence of severe events (hypoglycaemia or ketoacidosis) between the groups. We also found that the individuals who seem to benefit the most from CGM usage are those with MDI treatment having the relatively largest reduction in mean HbA1c. This is supported by RCT's and meta-analyses conducted since 2010 demonstrating that use of rtCGM improves glycaemic control in both children and adults with T1D in terms of lower HbA1c, increased time in range, reduced hypoglycaemia, and reduced glucose variability [220-225]. However, this contradicts some of our findings where we found an increased incidence of hypoglycaemias and ketoacidosis in patients with CSII and CGM. One explanation could be different indications for CGM and insulin pump treatment where patients with difficulties achieving the glucose target, having large glucose variability or frequent episodes with hypoglycaemia or ketoacidosis to a larger extent may have been offered CSII and CGM to improve their glucose balance.

Similar to our findings Zimmermann et al (2025) reported the highest HbA1c in the groups with the lowest usage of CGM indicating that CGM is an important factor in the achievement of glycaemic outcome [217]. Interestingly, they found that NDR-Swediabkids had the lowest event rate of ketoacidosis when compared with the other registers, and that this coincides with a high proportion who met the HbA1c target, a high proportion of CSII and CGM use, and strict national HbA1c recommendations of ≤48 mmol/mol [217]. It has previously been shown by Karges et al (2023) demonstrating evidence that an increase in diabetes technology decreases acute diabetes complications [226].

We also found that children with CGM were younger than children without CGM which is in line with the recommendations by the Swedish Association of Paediatric Endocrinology and Diabetes (SFPED) at that time. In 2015 there was a limited access to isCGM in Sweden and the diabetes teams had to select which patients who would benefit the most from the CGM systems.

The group of patients who ceased the use of CGM during this period we speculate had adverse effects with skin reactions and problems with eczema. Another reason could be difficulties remembering to calibrate the CGM device which forced the health care diabetes team to recommend the patient to stop CGM usage since the glucose values were not reliable. In some cases, patients and parents might experience an increased stress with all the information received from the CGM together with alarms signalling hypo- or hyperglycaemia leading to anxiety and unnecessary action due to fear of hypoglycaemia.

There is a variety of CGM metrics including Time in tight range, time below and above range, and glycaemic variability (SD) that are clinically useful and complement HbA1c in tracking glycaemic outcomes and making effective therapy adjustments. Glycaemic variability is considered an important marker of glucose control and Time in tight range might even predict acute and long-term complications in a more effective way than HbA1c, since the same HbA1c value can include very different glucose variability (SD). Sundberg et al (2025) suggested that a realistic target for preschool children with access to technology and an experienced diabetes team could be at least half of the time in normoglycaemic range, i.e., >50% Time in tight range [82].

Effective interpretation of CGM data is time consuming but improves with clinical experience. Therefore, it is important that all members in the diabetes team are regularly updated on the new technology to support the patients and families in an effective way. The opportunity to follow the patient's glucose monitoring via internet-based systems has enabled the diabetes teams to have contact with families online which can be cost- and time effective when the resources are limited in the healthcare system. This proved to be valuable during the Covid pandemic in 2020 and is an alternative with long distances in some sparsely populated Regions as is the case in Region Jämtland Härjedalen. From an environmental perspective this is positive since digital visits decreases the need for transportations which in the northern part of Sweden can mean many miles by car.

Later advancements in technology with calibration-free rtCGM have contributed to an increase in rtCGM over the years, and the arrival of automated insulin delivery (AID) pumps that require a rtCGM to function has also contributed to this change. Our finding that rtCGM results in lower mean HbA1c compared to isCGM is similar to RCTs using the latest generation of rtCGM systems demonstrating positive effects on both HbA1c and Time in range in adolescents and young adults [227,228].

Regarding equality the patients with T1D in Sweden or their parents do not have any costs for technical device such as insulin pumps or CGM systems. However, socio-economic differences and parents with lower education can imply a stress when it comes to using advanced technology which they might find difficult and complicated. In 2024, almost all children and adolescents with T1D in Sweden had access to CGM [6], but the usage of insulin pumps still varies considerably between different counties and also between paediatric clinics with frequencies ranging from 40% to 100% in different Regions [6]. These differences remain largely unexplained and as mentioned earlier there is no correlation between mean HbA1c and frequency of usage of automated insulin delivery (AID) pumps that uses rtCGM to calculate the algorithms for insulin dosage. This indicates that diabetes technology is not the sole solution and emphasizes the role of the multidisciplinary teams. It is like having an electrical bicycle – you need to pedal but you get some help on the way.

Partial remission

Our finding that the frequency of partial remission has increased with approximately 5% between 2007-2020 coincides with the general decrease of mean HbA1c during the same period. At the same time there has been a rapid development in diabetes technology with an increase in usage of insulin pumps and CGM systems. We found that use of CSII seemed to contribute to a longer partial remission period among Swedish children with T1D. However, this contradicts a study by Boughton et al where intensive glucose control in youth 10-17 years with new-onset T1D with advanced hybrid closed-loop treatment for 24 months did not prevent the decline in residual C-peptide secretion [229].

Young age (0-6 years) at diabetes diagnosis was associated with lower frequency of partial remission which is consistent with other studies [109,230]. Grönberg et al. demonstrated that younger age at diagnosis predicted lower C-peptide levels, which could be explained by a more aggressive form of the disease or an overall lower β-cell mass in younger children [231]. Since younger children more often have DKA at diagnosis of T1D compared to older children and considering that they have a lower reserve of β-cells this could explain the lower frequency of partial remission.

In our study we found a sex difference where boys more often than girls entered partial remission as previously shown by Örtqvist et al. [109] and that boys had a longer duration of partial remission compared with girls as reported by Bober et al. [107]. A speculation is that the relative insulin resistance which is more pronounced in pubertal girls than in boys, may be associated with a more rapid increase of exogenous insulin requirement. We found that girls were approximately one year younger than boys at diagnosis of diabetes which could be explained by the relative insulin resistance which is more pronounced in pubertal girls than in boys [136]. However, younger age at onset could not explain the gender difference in partial remission rate in our study. Sex hormones e.g., oestrogens, disturbed IGF-1/GH balance leading to a decreased insulin sensitivity producing higher HbA1c at diagnosis and during treatment, and differences in distribution of body fat, coping mechanisms, and health-related quality of life may all affect glycaemic control and lower the chance to reach partial remission in girls compared with boys [232]. In our study, there were more girls than boys having CSII treatment, which could be due to members of the diabetes team providing them with insulin pumps to improve their glucose metabolic control.

The Diabetes Control and Complications Trial (DCCT) study showed that intensive insulin therapy reduced the risk of C-peptide loss by more than 50%, suggesting that metabolic control is associated with the maintenance of β-cell function [110]. C-peptide levels >0.2 nmol/L at diagnosis and during the first year reduced the incidence of microvascular complications (retinopathy) and severe hypoglycaemia [111,231]. In our study mean C-peptide levels were above this threshold during the first 2 years after diagnosis, but 40% had C-peptide levels <0.2 nmol/L which may increase the risk of long-term complications.

In our study, we compared the definition IDAA1c with the clinical definition used in Sweden at the time when the patients were diagnosed, which is not based on the degree of residual β-cell function. Since treatment with insulin pump is associated with lower insulin dose/kg/day compared to MDI treatment and the Swedish clinical definition is based on total insulin dose, this could affect the results. However, when comparing the median C-peptide levels in patients being in partial remission (PR) with those not achieving PR, we could demonstrate higher levels of median C-peptide in the PR groups regardless of definition. Therefore, we consider the Swedish clinical definition of PR easier to use in a clinical setting compared to IDAA1c which is proper to use in research.

The new therapy with monoclonal anti-CD3 antibodies (teplizumab) that was authorized by FDA in the United States in 2022 for the treatment of individuals with multiple autoantibodies and T1D in stage 2 has given hope since studies have shown that it may preserve some β-cell function for several years [113]. This has led to discussions in many countries whether to start screening programs of children at risk of developing T1D to identify them when they are in stage 2 (≥2 auto antibodies, abnormal blood sugar, but no symptoms). If screening programs are going to be implemented in Sweden, CGM systems will play an important role in detecting deteriorating glucose levels, and by following Time in tight range this can be discovered at an early stage which enables intervention therapy to preserve β-cell function.

C-peptide is without doubt an important hormone since it decreases the risk of hypoglycaemia, DKA, microvascular complications, glucose variability and studies have shown that a high level of C-peptide correlates to a low HbA1c [104,105]. In the future, it can be of value to measure the concentration to identify the patients who could benefit from available intervention therapies. However, considering the importance of wise choices in clinical practice it is not relevant to keep on measuring C-peptide after onset of T1D if the diagnosis is clear, since there is no approved therapy to preserve β-cells available in Sweden yet.

Life with type 1 diabetes

Overall, in our study both youths and parents experienced that the new technology facilitated everyday life, and they experienced increased freedom. Even though the youths emphasized the importance of increased freedom and independence, most of them declared that continued support from their parents still was very important. This is supported by other studies demonstrating that parental involvement is important during adolescence [173-177]. Although the parents also experienced increased freedom with the new technology some of them expressed feelings of stress when it was not working, and this corroborates a study from Sassman et al. [233].

The opportunity for parents to follow their youth's CGM values from a distance made it easier to have control over glucose values without having to call or send text messages which is previously demonstrated by Fremont et al. [234]. Similar to our study they showed that remote glucose monitoring may facilitate youth independence by providing a way for them to stay connected to the support system while acquiring developmentally

appropriate skills, however emphasizing the importance to discuss boundaries to avoid parental over-involvement [234]. In a previous study by Cameron et al they reported that adolescents with parents who were perceived to be overinvolved in diabetes care have worse glycaemic outcome [185].

However, it is a challenge for the parents to balance between being supportive with continued control and at the same time letting their youth take more responsibility when emerging into adulthood. In our study most youths had no problem with parents following their CGM values, however there was one youth expressing feelings of being controlled in a negative way.

Parents experienced that CGM with alarm function gave them increased security and improved sleep at night which made them more satisfied and increased their quality of life which is in line with other studies [235-237]. The positive effect of the new technology on parents sleep is of importance since Lindström et al demonstrated in 2017 [186], that there is an increased risk of exhaustion depression in especially mothers of children with T1D, and we find this to be very important both on an individual level but also from a societal perspective as it may lead to less parents on sick leave thus possibly impacting the social security system.

The youths experienced increased satisfaction, security and more stable glucose values which has previously been described by Kulzer et al in 2021 [238], and Laffel et al [68] who demonstrated in randomized clinical trials that the use of CGM in young adults improved HbA1c compared to standard blood glucose finger pricks.

Support from health care

Both youths and parents had positive experiences of the diabetes teams with easy accessibility and continuity, and they emphasized the importance of technical support. In contrast to our study, other studies have shown that many adolescents with T1D and their parents report significant problems in communication with health-care providers, with a mismatch in perceived priorities [190], and difficulties getting the information they need to effectively manage their diabetes [191].

With the rapid development in technology during the last decade the members of the diabetes team have a challenge to stay informed about the new devices to be able to support patients and families. One parent highlighted that the interest and knowledge in technical devices varies between the members of the diabetes team and that it also can vary between different diabetes clinics in Sweden. This can lead to differences in the care for children and adolescents across the country which is also illustrated by the varying insulin pumps use in Swedish counties [239].

In Sweden the National Diabetes Register (NDR-Swediabkids) arranged improvement collaboratives (called IQ-projects) where all paediatric diabetes teams were invited to participate. They started in 2011, and since then most of the 43 paediatric diabetes teams have participated leading to an improved and more equal health care [240]. Interestingly mean HbA1c decreased in both participating and non-participating centres

in Sweden, thereby indicating an improvement by a spatial spillover effect in non-participating centres [241]. At Östersund hospital we saw this gratifying spillover effect between the paediatric and the adult diabetes team when they improved their mean HbA1c after our participation in IQ-1.

Over the last decade, Sweden has experienced an improved glucose control with a lowering of mean HbA1c [239] which led to the decision by SFPED in 2017 to lower the glucose target to ≤48 mmol/mol for children and adolescents with T1D [242]. Most of the parents and youths had not reflected over the lowering of the glucose target, and they experienced that the gluco-metabolic measurement Time in tight range is more useful in everyday life than HbA1c. The finding that the lowering of the glucose target was not anything that the youths or parents had considered a problem is interesting since it was an intensive debate among Swedish paediatricians whether this might cause an increased stress for the families [24].

Some parents described feelings of failure if their youth did not reach the glucose target and the importance of the members in the diabetes team to offer relief. The importance of the diabetes teams is also showed by Jespersen et al in 2021 in a qualitative interview study about how families experience their outpatient paediatric diabetes visits [243]. Thus, the challenge for the members in the diabetes team is to keep the balance in supporting the increased independence of the youth and at the same time encourage the parents to continue to be supportive and engaged.

To summarise the findings in study I-IV, the evolution of technical devices has improved the opportunities for children and adolescents with T1D to achieve the glucose target and to reduce stress in the families. This enables healthcare to equalize socioeconomic differences, and the arrival of AID-pumps facilitates everyday life for patients with T1D and their parents who struggle 24 hours a day to keep the glucose level in target. The development of technology is driven by the demands from patients with T1D and their parents. This was demonstrated by parents who manipulated insulin-pumps themselves to create hybrid closed-loop insulin pumps in lack of CME-approved AID-pumps. Health care professionals did not approve this, but they still had to supply the families with technical devices making it possible. Companies have an economical interest in developing new technology since it is a large market with over 1.5 million children and adolescents with T1D in the world. A collaboration between representatives from patients, parents, healthcare and companies would be desirable to control the technological development. Even though there is a higher cost for the latest technical equipment this will most likely in the long run be cost effective due to less late complications and improved well-being for both patients and parents. The development of insulin pumps and CGM has been so rapid during the work with this thesis that the results now feel partly out of date, and until we have a cure, it is important that every child and adolescent in Sweden with T1D has the possibility to achieve the glycaemic target with professional support from the diabetes team and advanced technology to increase the equality in healthcare.

Strengths and limitations

A major strength in Paper I and II is the large number of patients with real life data which reflects reality in contrast to RCTs with limited numbers of patients. The Swedish National Diabetes Register for Children (NDR-Swediabkids) has a coverage of nearly 98% of prevalent cases which gives the study a good representation of the paediatric population with T1D in Sweden which increases the external validity.

Having both sexes in all analyses and the fact that everyone had access to the new technology is a strength in terms of equality.

A limitation is that we do not know the indication for patients starting CSII treatment or CGM, which could be due to poor glycaemic control, young age, patient preference, doctor's preference, frequent episodes of severe hypoglycaemia or ketoacidosis or a combination of all these factors. There is no standardised curriculum for when and how to initiate CGM- or insulin pump treatment so this varies between paediatric clinics. This could be a selection bias affecting the results.

In Paper I, the number of patients that changed insulin delivery method each year was quite large (10%), and we do not know the reason behind these changes. Most patients changed from MDI to CSII, and the frequency of insulin pump use increased by more than 50% during the study period. The group with missing data on HbA1c in the longitudinal cohort in paper I was quite large (21%), and this may be explained by a short diabetes duration, and young patients having extra visits without HbA1c testing. This could affect the internal validity. To the best of our knowledge, the distribution of missing data is unbiased.

A weakness in paper I and II is that we do not know which patients were using carbohydrate counting, which became an established method at all paediatric clinics during the study period. By using carbohydrate counting more accurate bolus doses of insulin can be administered leading to improved glycaemic control. This was not registered in NDR-Swediabkids until 2018 and could potentially affect the results as a confounder.

Another limitation is that data on the use of CGM was not registered in NDR-Swediabkids until 2016, and the use of both rtCGM and isCGM became more prevalent during the study period and in 2018 a majority (93%) of all children and adolescents with T1D used CGM. In Paper II, we intended to analyse the CGM metrics average sensor glucose, standard deviation (SD), and TITR but due to missing data this was not possible.

A limitation in Paper I, II, and III is that HbA1c analyses were performed at different hospitals, and even though the different laboratory methods are quality assured through Equalis (External Quality Assurance in Laboratory Medicine in Sweden) there are paediatric clinics having their own HbA1c testing equipment to enable capillary testing at the same day as the out-patient visit. Since we do not know how the registered HbA1c values are analysed this could affect the internal validity, but the results are un-biased.

A limitation in Paper III is that we do not have any valid blood glucose values when C-peptide was analysed one year after diagnosis of T1D as this blood sample was taken non-fasting and at a randomly chosen time and not after a mixed-meal tolerance test. Since the C-peptide level at diagnosis of T1D was analysed before administration of insulin, we assumed that the blood glucose level was very high. This affects the internal validity.

Another weakness is the potential bias due to the fact that registration of total daily insulin dose was based on recall at the time of the visit to the paediatric clinic as the use of internet-based systems to download data from insulin pumps was not yet in practice. However, we judge this not to cause bias.

The frequency of CSII usage increased during the study periods in Paper I, II, and III, and since there was a difference between different paediatric clinics this could be a bias in the analyses and is a weakness of the studies.

In Paper IV, the choice of a qualitative method with interviews gave us an opportunity to go deeper into the subject with supplementary questions, which is not possible using a survey. An advantage was that the participants could choose if they wanted a face-to-face interview or an interview on-line, which made it equally easy to participate for everybody in the area. Not conducting interviews face-to-face can be time- and cost effective and might enable participation despite long distances, and in an on-line interview you can observe body-language to some extent.

The use of an interview guide ensured similar questions and topics in all interviews and since the questions were not distributed beforehand this resulted in spontaneous answers which is preferable. We conducted a pilot-interview to test the interview guide to make sure that it gave rich answers correlating with the aim of the study which strengthened the credibility.

There is a potential risk of recruitment bias since the strategic selection of participants was made by the nurses in the diabetes team and they may have consciously or subconsciously, recruited patients and parents who would feel comfortable with an interview, and were somewhat satisfied with the clinical visits.

A strength is that by using the inclusion criteria and two different study cites, we covered different groups of the population and increased the credibility and the transferability of the study.

The inclusion of more than one researcher in the analysis strengthens dependability and by describing the process from recruiting the participants, through the analysis and production of finished result the reader can judge the study's transferability and credibility.

By presenting different steps and examples of the analysis and through clarifying the results in the text confirmed with quotations we further strengthened the dependability

and transferability. Quotations help to show that the text in the results comes from the collected data strengthening conformability as well as credibility.

The interviewer had pre-understanding and experience of working with patients with T1D and their parents which could be an advantage, but this could also affect the process by impeding certain follow-up questions that might have revealed interesting insights. A strength of the study is that the interviewer did not know the informants who saw other paediatricians at the out-patient visits.

Conclusions

I: There was a small decrease in HbA1c with CSII treatment compared to MDI treatment, but this is judged to be of little clinical relevance. Overall, there was a general reduction in HbA1c between 2011 and 2016 irrespective of insulin delivery method without increased incidences of severe hypoglycaemia.

II: CGM decreased HbA1c compared to self-monitored blood glucose and the combination of rtCGM and MDI treatment resulted in the relatively largest reduction.

III: MDI treatment, longer diabetes duration, and female sex were associated with a lower frequency of partial remission. CSII treatment seemed to contribute to longer partial remission.

IV: New technology with insulin pumps and CGM facilitates everyday life for both youths with T1D and their parents but challenges the diabetes teams to support them by being updated with the rapid technical development. The study emphasizes the importance of support to the parents during the transition process to enable the youths to gradually take over responsibility for their diabetes and to maintain the glucose targets as young adults.
The opportunity for the parents to follow their youth's glucose values via an app in their mobile phones does not seem to be a problem to the youths who instead experience a feeling of increased security. The lowering of the glucose target in 2017 from <52 mmol/mol to ≤48 mmol/mol is not anything that neither youth nor parents have had much concern about, and they consider the gluco-metabolic measurement Time in tight range to be more useful in everyday life.

Future perspectives

The increased costs for diabetes technology might be balanced for society by a lowering of the costs in the social security system for parental sick-leave, through a higher number of work participation, and by increased quality-adjusted life years (QUALY). Therefore, it would be of interest to evaluate the finding that parents of children with T1D experience better sleep at night and decreased stress in the family with the use of new technology. Since it has previously been shown that especially mothers of a child with T1D have an increased risk of burn-out depression, it would be interesting to investigate whether the new diabetes technology has led to a change. By studying data from the Social longitudinal integrated database for health insurance and labour market studies (LISA) and NDR-Swediabkids, there is an opportunity to study if costs for sick-leave to parents of children with T1D has decreased parallel with the introduction of new diabetes technology.

The rapid development and increasing use of AID-pumps where some studies indicate that they improve glycaemic control without increasing BMI-SDS implies a need for further studies. Since obesity leads to an increased risk of cardiovascular disease the combination with T1D is undesirable and if this can be avoided the higher cost for AID-pumps can be justified. Further development of the AID-systems could include facilitating carbohydrate counting before meals by using the camera in the smart phone and then let artificial intelligence calculate an appropriate bolus dose.

Since the young adults worsen their glycaemic control during the transition to adult care even though they have access to the latest technology, it would be of interest to investigate factors that could support and facilitate this transition. How should the diabetes teams act to support them and their parents during the time at the paediatric clinic to balance between independence and control.
It would be interesting to do a qualitative interview study with young adults and diabetes nurses at the adult diabetes clinic to capture their experiences from the transition care. This could potentially lead to an improved co-operation between the paediatric and adult clinic and the results as e.g., mean HbA1c can be studied with data from NDR.

The arrival of potential preventive treatment with monoclonal anti-CD3 antibodies (Teplizumab) to preserve β-cell mass has highlighted the importance of CGM to identify the individuals at risk of developing T1D. The intervention group would be children and adolescents in stage 2 i.e., with ≥2 auto antibodies, abnormal glucose levels, but no symptoms. It would be of interest to develop methods to measure C-peptide in an easier way and this may be possible with capillary blood on filter paper that could be done in a home environment. Analysis of C-peptide is needed if screening and intervention are going to be implemented into healthcare in the future. A collaboration between the clinical chemical laboratories and paediatric clinics in Östersund and Örebro hospital has been discussed to study if the method with analysis on filter paper is reliable.

Acknowledgements

I wish to express my sincere gratitude to all those who have guided, supported and assisted me during the completion of this thesis.

First, I want to thank all the adolescents and their parents, for their collaboration in the qualitative study.

My special thanks are also due to:

Torbjörn Lind, my main supervisor and mentor in scientific work, for your never-ending support, encouragement and thoroughness. Your profound knowledge in scientific work and endless patience for questions and discussions has been invaluable.

Mikael Lilja, my co-supervisor who introduced me into science, being my main supervisor in the beginning of this work, for your contagious enthusiasm, support, and long-standing devotion to improvement of diabetes care.

Stefan Särnblad, my co-supervisor who encouraged me to start this project, for your deep knowledge in paediatric diabetology, for fruitful discussions and for being an eminent proofreader of the manuscripts.

Ulf Samuelsson, my co-supervisor who gave me the opportunity to start this project, for your patience and support working together in Linköping and for sharing your knowledge and long experience in clinic paediatric diabetology and research.

Marie Bladh, statistician at Linköping University, for helping me with the statistics and for many interesting discussions about research and things in life. I am so grateful for your friendship and appreciate your generosity and support.

Rita Sjöström, my co-supervisor in the qualitative study, for guiding me into the world of qualitative research and for your invaluable support, enthusiasm, and encouragement.

Anna Lindam, statistician for constructive criticism and reviewing the thesis.

The Swedish Childhood Diabetes Register group in Umeå led by **Torbjörn Lind** with **Anna Möllsten**, **Ingeborg Waernbaum**, **Staffan Schön**, **Katarina Steen-Carlsson**, **Marie Fredriksson, Cecilia Toppe**, and **Emma Persson**, for inviting me to be a part of their collaboration with many fruitful discussions during workshops and meetings with valuable input on my research questions.

The Expert group for NDR-Swediabkids led by **Karin Åkesson**, for letting me be part of this group of highly competent members, with **Stefan Särnblad**, **Ragnar Hanås**, **Auste Pundzuite-Lyckå**, **Elisabeth Jelleryd**, and **Ebba Linder** which made me interested in research on data from the register.

All the members of the diabetes team at the Department of Paediatrics, Östersund hospital, **Carina Bodén**, **Tina Jonsson**, **Helene Magnusson**, **Annika Paulsson**, **Ann-Sofie Svanberg**, **Jessica Åkermo**, **Linda Hansson**, **Love Brande**, and **Maja Lugnet**, for taking care of all the patients during this time when I have been finishing my thesis.

Anu Käll and **Djenni Arntsen**, medical secretaries, for helping me with the transcriptions of the interviews in the qualitative study.

My friends and colleagues at the Department of Paediatrics, Östersund hospital for good friendship, support and inspiration, and especially my colleagues sharing an interest in research **Estelle Naumburg**, **Gustaf Tanghøj**, **Tommie Irewall**, **Samuel Videholm**, **Viktor Grut**, and **Sofia Sollander** for interesting discussions and contributions to the scientific environment at our department.

Urban Tirén, former head of the Department of Paediatrics, Östersund Hospital, for giving me the opportunity to begin with the scientific studies, and for being a wise, devoted paediatrician always willing to share your great knowledge with everyone.

Eva Strömberg, present head of the Department of Paediatrics, Östersund Hospital, and **Annalena Joelsson** and **Catrin Holgén**, former managers for the section for paediatricians, Östersund Hospital, for giving me the opportunity to interrupt the clinical work and concentrate on the scientific studies.

Yonas Berhan, **Anna Möllsten**, and **Christina West** for reviewing the thesis.

All my **dear friends** for being who you are and making life joyful and happy!

My sisters, **Karin Dannaeus**, for inspiring me into research, and for being supportive, encouraging and understanding in moments of despair, and **Kristina Dannaeus**, for all the things you do at Harvik and for being a wonderful aunt to our children.

Margareta Dannaeus, my dear mother, for always believing in me. **Anders Dannaeus**, my late father who gave me inspiration to choose medical studies and paediatrics.

Erik, Elsa, **Alva** and **Hanna,** my beloved children and joy of life, for making the family grow with husband, fiancée, boyfriends, grandchild, and a dog. Family is forever!

Håkan, my husband, for all your love and support, and for your patience during times when I have been preoccupied with the studies. Your extensive knowledge in endocrinology and diabetes has been helpful in numerous discussions over the years, and you have been a valuable reader of the thesis.

This thesis was financially supported by the Research and Development Unit, Region Jämtland Härjedalen, Stiftelsen Samariten, Thuringstiftelsen, Oskarfonden, Visare Norr, Kvinnliga Föreningen Gamla Östersund, and Svenska Diabetesstiftelsen.

References

1. International Diabetes Federation (IDF). (2025).
2. NDR-SWEDIABKIDS. Swedish National Quality Register for Diabetes in Children and Adolescents. (2023).
3. Pickup, J.C., Keen, H., Parsons, J.A. & Alberti, K.G. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br Med J* **1**, 204-207 (1978).
4. Sherr, J.L.*, et al.* ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Insulin delivery. *Pediatr Diabetes* **23**, 1406-1431 (2022).
5. Szypowska, A.*, et al.* Insulin pump therapy in children with type 1 diabetes: analysis of data from the SWEET registry. *Pediatr Diabetes* **17 Suppl 23**, 38-45 (2016).
6. NDR-SWEDIABKIDS. Swedish Childhood Diabetes Register. Vol. 2024 (2024).
7. Dovc, K., Bode, B.W. & Battelino, T. Continuous and Intermittent Glucose Monitoring in 2021. *Diabetes Technol Ther* **24**, S209-S219 (2022).
8. Swedish Comments to ISPAD Guidelines (SFPED). Vol. 2025 (2024).
9. Diabetes (type 1 and type 2) in children and young people: diagnosis and management UK: National Institute for Care Excellence (NICE). (2015).
10. de Bock, M.*, et al.* International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2024: Glycemic Targets. *Horm Res Paediatr* **97**, 546-554 (2024).
11. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* **329**, 977-986 (1993).
12. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J Pediatr* **125**, 177-188 (1994).
13. Diabetes Control and Complications Trial/Epidemiology of Diabetes, Interventions and Complications Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. *Diabetes Care* **39**, 686-693 (2016).
14. American Diabetes Association Professional Practice, C. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care* **45**, S17-S38 (2022).
15. Shah, V.N.*, et al.* Continuous Glucose Monitoring Profiles in Healthy Nondiabetic Participants: A Multicenter Prospective Study. *J Clin Endocrinol Metab* **104**, 4356-4364 (2019).
16. Lind, M.*, et al.* Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med* **371**, 1972-1982 (2014).

17. Abraham, M.B.*, et al.* ISPAD Clinical Practice Consensus Guidelines 2022: Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* **23**, 1322-1340 (2022).
18. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, G., Fox, L.A., Beck, R.W. & Xing, D. Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. *Diabetes Care* **33**, 1297-1299 (2010).
19. Patton, S.R., Dolan, L.M., Henry, R. & Powers, S.W. Parental fear of hypoglycemia: young children treated with continuous subcutaneous insulin infusion. *Pediatr Diabetes* **8**, 362-368 (2007).
20. Johnson, S.R., Cooper, M.N., Davis, E.A. & Jones, T.W. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. *Diabet Med* **30**, 1126-1131 (2013).
21. Haugstvedt, A., Wentzel-Larsen, T., Graue, M., Sovik, O. & Rokne, B. Fear of hypoglycaemia in mothers and fathers of children with Type 1 diabetes is associated with poor glycaemic control and parental emotional distress: a population-based study. *Diabet Med* **27**, 72-78 (2010).
22. Clarke, W., Jones, T., Rewers, A., Dunger, D. & Klingensmith, G.J. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* **10 Suppl 12**, 134-145 (2009).
23. Seaquist, E.R.*, et al.* Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* **36**, 1384-1395 (2013).
24. Ludvigsson, J. Är HbA1c 40 mmol/mol tecken på god diabetesvård? *Läkartidningen* (2013).
25. Glaser, N.*, et al.* ISPAD clinical practice consensus guidelines 2022: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes* **23**, 835-856 (2022).
26. Hanas, R. & Ludvigsson, J. Hypoglycemia and ketoacidosis with insulin pump therapy in children and adolescents. *Pediatr Diabetes* **7 Suppl 4**, 32-38 (2006).
27. Donaghue, K.C., Chiarelli, F., Trotta, D., Allgrove, J. & Dahl-Jorgensen, K. Microvascular and macrovascular complications associated with diabetes in children and adolescents. *Pediatr Diabetes* **10 Suppl 12**, 195-203 (2009).
28. Samuelsson, U., Steineck, I. & Gubbjornsdottir, S. A high mean-HbA1c value 3-15 months after diagnosis of type 1 diabetes in childhood is related to metabolic control, macroalbuminuria, and retinopathy in early adulthood--a pilot study using two nation-wide population based quality registries. *Pediatr Diabetes* **15**, 229-235 (2014).
29. Lachin, J.M., Orchard, T.J., Nathan, D.M. & Group, D.E.R. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* **37**, 39-43 (2014).
30. Jarvisalo, M.J.*, et al.* Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. *Circulation* **109**, 1750-1755 (2004).
31. Larsen, J.R.*, et al.* Intracoronary ultrasound examinations reveal significantly more advanced coronary atherosclerosis in people with type 1 diabetes than in age- and sex-matched non-diabetic controls. *Diab Vasc Dis Res* **4**, 62-65 (2007).

32. Margeirsdottir, H.D., Stensaeth, K.H., Larsen, J.R., Brunborg, C. & Dahl-Jorgensen, K. Early signs of atherosclerosis in diabetic children on intensive insulin treatment: a population-based study. *Diabetes Care* **33**, 2043-2048 (2010).
33. Laing, S.P.*, et al.* Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* **46**, 760-765 (2003).
34. Prahalad, P., Tanenbaum, M., Hood, K. & Maahs, D.M. Diabetes technology: improving care, improving patient-reported outcomes and preventing complications in young people with Type 1 diabetes. *Diabet Med* **35**, 419-429 (2018).
35. Tamborlane, W.V., Sherwin, R.S., Genel, M. & Felig, P. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N Engl J Med* **300**, 573-578 (1979).
36. Adolfsson, P., Ziegler, R. & Hanas, R. Continuous subcutaneous insulin infusion: Special needs for children. *Pediatr Diabetes* **18**, 255-261 (2017).
37. Swedish Agency for Health Technology and Assessment of Social Services (Statens beredning flr medicinsk utvärdering, S. Insulin pumps for diabetes (Insulinpumpar vid diabetes). Vol. 2025 (2013).
38. Cummins, E.*, et al.* Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess* **14**, iii-iv, xi-xvi, 1-181 (2010).
39. Scuffham, P. & Carr, L. The cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for the management of diabetes. *Diabet Med* **20**, 586-593 (2003).
40. Palmer, A.J., Roze, S., Valentine, W.J. & Spinas, G. The cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for the management of diabetes: response to Scuffham [corrected] and Carr. *Diabet Med* **21**, 1372; author reply 1372-1373 (2004).
41. Samuelsson, U.*, et al.* Teenage girls with type 1 diabetes have poorer metabolic control than boys and face more complications in early adulthood. *J Diabetes Complications* **30**, 917-922 (2016).
42. Pickup, J., Mattock, M. & Kerry, S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* **324**, 705 (2002).
43. Weissberg-Benchell, J., Antisdel-Lomaglio, J. & Seshadri, R. Insulin pump therapy: a meta-analysis. *Diabetes Care* **26**, 1079-1087 (2003).
44. Sulli, N. & Shashaj, B. Continuous subcutaneous insulin infusion in children and adolescents with diabetes mellitus: decreased HbA1c with low risk of hypoglycemia. *J Pediatr Endocrinol Metab* **16**, 393-399 (2003).
45. Jeha, G.S.*, et al.* Insulin pump therapy in preschool children with type 1 diabetes mellitus improves glycemic control and decreases glucose excursions and the risk of hypoglycemia. *Diabetes Technol Ther* **7**, 876-884 (2005).
46. Berghaeuser, M.A.*, et al.* Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. *Pediatr Diabetes* **9**, 590-595 (2008).

47. Jakisch, B.I., *et al.* Comparison of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in paediatric Type 1 diabetes: a multicentre matched-pair cohort analysis over 3 years. *Diabet Med* **25**, 80-85 (2008).
48. Ahern, J.A., *et al.* Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatr Diabetes* **3**, 10-15 (2002).
49. Plotnick, L.P., Clark, L.M., Brancati, F.L. & Erlinger, T. Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care* **26**, 1142-1146 (2003).
50. Skogsberg, L., *et al.* Improved treatment satisfaction but no difference in metabolic control when using continuous subcutaneous insulin infusion vs. multiple daily injections in children at onset of type 1 diabetes mellitus. *Pediatr Diabetes* **9**, 472-479 (2008).
51. Brorsson, A.L., Viklund, G., Ortqvist, E. & Lindholm Olinder, A. Does treatment with an insulin pump improve glycaemic control in children and adolescents with type 1 diabetes? A retrospective case-control study. *Pediatr Diabetes* **16**, 546-553 (2015).
52. Wheeler, B.J., Heels, K., Donaghue, K.C., Reith, D.M. & Ambler, G.R. Insulin pump-associated adverse events in children and adolescents--a prospective study. *Diabetes Technol Ther* **16**, 558-562 (2014).
53. Guenego, A., *et al.* Insulin Pump Failures: Has There Been an Improvement? Update of a Prospective Observational Study. *Diabetes Technol Ther* **18**, 820-824 (2016).
54. Heinemann, L. & Krinelke, L. Insulin infusion set: the Achilles heel of continuous subcutaneous insulin infusion. *J Diabetes Sci Technol* **6**, 954-964 (2012).
55. Heinemann, L., Walsh, J. & Roberts, R. We Need More Research and Better Designs for Insulin Infusion Sets. *J Diabetes Sci Technol* **8**, 199-202 (2014).
56. Heinemann, L. Insulin Infusion Sets: A Critical Reappraisal. *Diabetes Technol Ther* **18**, 327-333 (2016).
57. Kordonouri, O., Lauterborn, R. & Deiss, D. Lipohypertrophy in young patients with type 1 diabetes. *Diabetes Care* **25**, 634 (2002).
58. Kordonouri, O., *et al.* Lipoatrophy in children with type 1 diabetes: an increasing incidence? *J Diabetes Sci Technol* **9**, 206-208 (2015).
59. Burgmann, J., Biester, T., Grothaus, J., Kordonouri, O. & Ott, H. Pediatric diabetes and skin disease (PeDiSkin): A cross-sectional study in 369 children, adolescents and young adults with type 1 diabetes. *Pediatr Diabetes* **21**, 1556-1565 (2020).
60. Berg, A.K., *et al.* High frequencies of dermatological complications in children using insulin pumps or sensors. *Pediatr Diabetes* **19**, 733-740 (2018).
61. Haller, M.J., Stalvey, M.S. & Silverstein, J.H. Predictors of control of diabetes: monitoring may be the key. *J Pediatr* **144**, 660-661 (2004).
62. Ziegler, R., *et al.* Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. *Pediatr Diabetes* **12**, 11-17 (2011).
63. Miller, K.M., *et al.* Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care* **36**, 2009-2014 (2013).

64. Ortiz La Banca, R.*, et al.* Blood glucose monitoring (BGM) still matters for many: Associations of BGM frequency and glycemic control in youth with type 1 diabetes. *Prim Care Diabetes* **15**, 832-836 (2021).
65. Tauschman, M.*, et al.* International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2024 Diabetes Technologies: Glucose Monitoring. *Horm Res Paediatr* **97**, 615-635 (2024).
66. Jendrike, N., Baumstark, A., Kamecke, U., Haug, C. & Freckmann, G. ISO 15197: 2013 Evaluation of a Blood Glucose Monitoring System's Measurement Accuracy. *J Diabetes Sci Technol* **11**, 1275-1276 (2017).
67. Cardona-Hernandez, R.*, et al.* Glycemic Outcome Associated With Insulin Pump and Glucose Sensor Use in Children and Adolescents With Type 1 Diabetes. Data From the International Pediatric Registry SWEET. *Diabetes Care* **44**, 1176-1184 (2021).
68. Laffel, L.M.*, et al.* Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial. *JAMA* **323**, 2388-2396 (2020).
69. Haskova, A.*, et al.* Real-time CGM Is Superior to Flash Glucose Monitoring for Glucose Control in Type 1 Diabetes: The CORRIDA Randomized Controlled Trial. *Diabetes Care* **43**, 2744-2750 (2020).
70. Visser, M.M.*, et al.* Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. *Lancet* **397**, 2275-2283 (2021).
71. Marigliano, M.*, et al.* Association of the use of diabetes technology with HbA1c and BMI-SDS in an international cohort of children and adolescents with type 1 diabetes: The SWEET project experience. *Pediatr Diabetes* **22**, 1120-1128 (2021).
72. van den Boom, L.*, et al.* Use of Continuous Glucose Monitoring in Pump Therapy Sensor Augmented Pump or Automated Insulin Delivery in Different Age Groups (0.5 to <26 Years) With Type 1 Diabetes From 2018 to 2021: Analysis of the German/Austrian/Swiss/Luxemburg Diabetes Prospective Follow-up Database Registry. *J Diabetes Sci Technol* **18**, 1122-1131 (2024).
73. Ebekozien, O.*, et al.* Longitudinal Trends in Glycemic Outcomes and Technology Use for Over 48,000 People with Type 1 Diabetes (2016-2022) from the T1D Exchange Quality Improvement Collaborative. *Diabetes Technol Ther* **25**, 765-773 (2023).
74. Zeng, B., Gao, L., Yang, Q., Jia, H. & Sun, F. Automated Insulin Delivery Systems in Children and Adolescents With Type 1 Diabetes: A Systematic Review and Meta-analysis of Outpatient Randomized Controlled Trials. *Diabetes Care* **46**, 2300-2307 (2023).
75. Michou, P., Gkiourtzis, N., Christoforidis, A., Kotanidou, E.P. & Galli-Tsinopoulou, A. The efficacy of automated insulin delivery systems in children and adolescents with type 1 diabetes Mellitus: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* **199**, 110678 (2023).
76. Abraham, M.B.*, et al.* Effect of a Hybrid Closed-Loop System on Glycemic and Psychosocial Outcomes in Children and Adolescents With Type 1 Diabetes: A Randomized Clinical Trial. *JAMA Pediatr* **175**, 1227-1235 (2021).

77. Bunn, H.F., Gabbay, K.H. & Gallop, P.M. The glycosylation of hemoglobin: relevance to diabetes mellitus. *Science* **200**, 21-27 (1978).
78. Nathan, D.M. & Group, D.E.R. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* **37**, 9-16 (2014).
79. Beck, R.W., Connor, C.G., Mullen, D.M., Wesley, D.M. & Bergenstal, R.M. The Fallacy of Average: How Using HbA(1c) Alone to Assess Glycemic Control Can Be Misleading. *Diabetes Care* **40**, 994-999 (2017).
80. Chehregosha, H., Khamseh, M.E., Malek, M., Hosseinpanah, F. & Ismail-Beigi, F. A View Beyond HbA1c: Role of Continuous Glucose Monitoring. *Diabetes Ther* **10**, 853-863 (2019).
81. Battelino, T.*, et al.* Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care* **42**, 1593-1603 (2019).
82. Sundberg, F., Smart, C.E., Samuelsson, J., Akesson, K. & Krogvold, L. Using Time in Tight Glucose Range as a Health-Promoting Strategy in Preschoolers With Type 1 Diabetes. *Diabetes Care* **48**, 6-14 (2025).
83. Castaneda, J., Arrieta, A., van den Heuvel, T., Battelino, T. & Cohen, O. Time in Tight Glucose Range in Type 1 Diabetes: Predictive Factors and Achievable Targets in Real-World Users of the MiniMed 780G System. *Diabetes Care* **47**, 790-797 (2024).
84. Beck, R.W. Is It Time to Replace Time-in-Range with Time-in-Tight-Range? Maybe Not. *Diabetes Technol Ther* **26**, 147-150 (2024).
85. Petersson, J., Akesson, K., Sundberg, F. & Sarnblad, S. Translating glycated hemoglobin A1c into time spent in glucose target range: A multicenter study. *Pediatr Diabetes* **20**, 339-344 (2019).
86. Beck, R.W.*, et al.* Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes Care* **42**, 400-405 (2019).
87. Fonolleda, M., Murillo, M., Vazquez, F., Bel, J. & Vives-Pi, M. Remission Phase in Paediatric Type 1 Diabetes: New Understanding and Emerging Biomarkers. *Horm Res Paediatr* **88**, 307-315 (2017).
88. Couper, J.J.*, et al.* ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes* **19 Suppl 27**, 20-27 (2018).
89. Ludvigsson, J. & Heding, L.G. C-peptide in children with juvenile diabetes. A preliminary report. *Diabetologia* **12**, 627-630 (1976).
90. Knip, M.*, et al.* Postinitial remission in diabetic children--an analysis of 178 cases. *Acta Paediatr Scand* **71**, 901-908 (1982).
91. Knip, M., Puukka, R., Kaar, M.L. & Akerblom, H.K. Remission phase, endogenous insulin secretion and metabolic control in diabetic children. *Acta Diabetol Lat* **19**, 243-251 (1982).
92. Lombardo, F.*, et al.* Two-year prospective evaluation of the factors affecting honeymoon frequency and duration in children with insulin dependent diabetes mellitus: the key-role of age at diagnosis. *Diabetes Nutr Metab* **15**, 246-251 (2002).
93. Steiner, D.F., Cunningham, D., Spigelman, L. & Aten, B. Insulin biosynthesis: evidence for a precursor. *Science* **157**, 697-700 (1967).

94. Palmer, J.P., *et al.* C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. *Diabetes* **53**, 250-264 (2004).
95. Madsbad, S., *et al.* Prevalence of residual beta-cell function in insulin-dependent diabetics in relation to age at onset and duration of diabetes. *Diabetes* **27 Suppl 1**, 262-264 (1978).
96. Ludvigsson, J., *et al.* Decline of C-peptide during the first year after diagnosis of Type 1 diabetes in children and adolescents. *Diabetes Res Clin Pract* **100**, 203-209 (2013).
97. Lachin, J.M., McGee, P., Palmer, J.P. & Group, D.E.R. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes* **63**, 739-748 (2014).
98. Greenbaum, C.J., *et al.* Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes* **61**, 2066-2073 (2012).
99. Palmer, J.P. C-peptide in the natural history of type 1 diabetes. *Diabetes Metab Res Rev* **25**, 325-328 (2009).
100. Keenan, H.A., *et al.* Residual insulin production and pancreatic ss-cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes* **59**, 2846-2853 (2010).
101. Oram, R.A., *et al.* The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. *Diabetologia* **57**, 187-191 (2014).
102. Williams, K.V., Becker, D.J., Orchard, T.J. & Costacou, T. Persistent C-peptide levels and microvascular complications in childhood onset type 1 diabetes of long duration. *J Diabetes Complications* **33**, 657-661 (2019).
103. Wang, L., Lovejoy, N.F. & Faustman, D.L. Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. *Diabetes Care* **35**, 465-470 (2012).
104. Kunt, T., *et al.* The effect of human proinsulin C-peptide on erythrocyte deformability in patients with Type I diabetes mellitus. *Diabetologia* **42**, 465-471 (1999).
105. Ludvigsson, J. The clinical potential of low-level C-peptide secretion. *Expert Rev Mol Diagn* **16**, 933-940 (2016).
106. Forst, T., Kunt, T., Wilhelm, B., Weber, M.M. & Pfutzner, A. Role of C-Peptide in the regulation of microvascular blood flow. *Exp Diabetes Res* **2008**, 176245 (2008).
107. Bober, E., Dundar, B. & Buyukgebiz, A. Partial remission phase and metabolic control in type 1 diabetes mellitus in children and adolescents. *J Pediatr Endocrinol Metab* **14**, 435-441 (2001).
108. Bowden, S.A., Duck, M.M. & Hoffman, R.P. Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. *Pediatr Diabetes* **9**, 197-201 (2008).
109. Ortqvist, E., Falorni, A., Scheynius, A., Persson, B. & Lernmark, A. Age governs gender-dependent islet cell autoreactivity and predicts the clinical course in childhood IDDM. *Acta Paediatr* **86**, 1166-1171 (1997).
110. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized,

controlled trial. The Diabetes Control and Complications Trial Research Group. *Ann Intern Med* **128**, 517-523 (1998).
111. Steffes, M.W., Sibley, S., Jackson, M. & Thomas, W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* **26**, 832-836 (2003).
112. Besser, R.E.J.*, et al*. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes* **23**, 1175-1187 (2022).
113. Sims, E.K.*, et al*. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med* **13**(2021).
114. Besser, R.E., Shields, B.M., Casas, R., Hattersley, A.T. & Ludvigsson, J. Lessons from the mixed-meal tolerance test: use of 90-minute and fasting C-peptide in pediatric diabetes. *Diabetes Care* **36**, 195-201 (2013).
115. Abdul-Rasoul, M., Habib, H. & Al-Khouly, M. 'The honeymoon phase' in children with type 1 diabetes mellitus: frequency, duration, and influential factors. *Pediatr Diabetes* **7**, 101-107 (2006).
116. Mortensen, H.B.*, et al*. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care* **32**, 1384-1390 (2009).
117. Nwosu, B.U. Partial Clinical Remission of Type 1 Diabetes Mellitus in Children: Clinical Applications and Challenges with its Definitions. *Eur Med J Diabetes* **4**, 89-98 (2019).
118. Nielens, N., Polle, O., Robert, A. & Lysy, P.A. Integration of Routine Parameters of Glycemic Variability in a Simple Screening Method for Partial Remission in Children with Type 1 Diabetes. *J Diabetes Res* **2018**, 5936360 (2018).
119. Lundberg, R.L.*, et al*. Partial clinical remission in type 1 diabetes: a comparison of the accuracy of total daily dose of insulin of <0.3 units/kg/day to the gold standard insulin-dose adjusted hemoglobin A1c of </=9 for the detection of partial clinical remission. *J Pediatr Endocrinol Metab* **30**, 823-830 (2017).
120. Couper, J., Donaghue, K., International Society for, P. & Adolescent, D. Phases of diabetes. *Pediatr Diabetes* **8**, 44-47 (2007).
121. Sjöblad, S. *Barn- och ungdomsdiabetes*, (Studentlitteratur, 2008).
122. Persson, M.*, et al*. The Better Diabetes Diagnosis (BDD) study - A review of a nationwide prospective cohort study in Sweden. *Diabetes Res Clin Pract* **140**, 236-244 (2018).
123. Kueh, M.T.W., Chew, N.W.S., Al-Ozairi, E. & le Roux, C.W. The emergence of obesity in type 1 diabetes. *Int J Obes (Lond)* **48**, 289-301 (2024).
124. Verbeeten, K.C., Elks, C.E., Daneman, D. & Ong, K.K. Association between childhood obesity and subsequent Type 1 diabetes: a systematic review and meta-analysis. *Diabet Med* **28**, 10-18 (2011).
125. Zucker, I.*, et al*. Obesity in late adolescence and incident type 1 diabetes in young adulthood. *Diabetologia* **65**, 1473-1482 (2022).
126. Blom, L., Persson, L.A. & Dahlquist, G. A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* **35**, 528-533 (1992).
127. Wilkin, T.J. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia* **44**, 914-922 (2001).
128. Karlberg, J., Luo, Z.C. & Albertsson-Wikland, K. Body mass index reference values (mean and SD) for Swedish children. *Acta Paediatr* **90**, 1427-1434 (2001).

129. Amiel, S.A., *et al.* Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. *J Clin Endocrinol Metab* **72**, 277-282 (1991).
130. Caprio, S., *et al.* Effects of puberty and diabetes on metabolism of insulin-sensitive fuels. *Am J Physiol* **266**, E885-891 (1994).
131. Caprio, S. Insulin: the other anabolic hormone of puberty. *Acta Paediatr Suppl* **88**, 84-87 (1999).
132. Moran, A., *et al.* Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* **48**, 2039-2044 (1999).
133. Cook, J.S., Hoffman, R.P., Stene, M.A. & Hansen, J.R. Effects of maturational stage on insulin sensitivity during puberty. *J Clin Endocrinol Metab* **77**, 725-730 (1993).
134. Amiel, S.A., Sherwin, R.S., Simonson, D.C., Lauritano, A.A. & Tamborlane, W.V. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* **315**, 215-219 (1986).
135. Arslanian, S., Nixon, P.A., Becker, D. & Drash, A.L. Impact of physical fitness and glycemic control on in vivo insulin action in adolescents with IDDM. *Diabetes Care* **13**, 9-15 (1990).
136. Arslanian, S.A., Heil, B.V., Becker, D.J. & Drash, A.L. Sexual dimorphism in insulin sensitivity in adolescents with insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* **72**, 920-926 (1991).
137. Acerini, C.L., Cheetham, T.D., Edge, J.A. & Dunger, D.B. Both insulin sensitivity and insulin clearance in children and young adults with type I (insulin-dependent) diabetes vary with growth hormone concentrations and with age. *Diabetologia* **43**, 61-68 (2000).
138. Halldin, M.U., Hagenas, L., Tuvemo, T. & Gustafsson, J. Profound changes in the GH-IGF-I system in adolescent girls with IDDM: can IGFBP1 be used to reflect overall glucose regulation? *Pediatr Diabetes* **1**, 121-130 (2000).
139. van der Sluis, I.M., de Ridder, M.A., Boot, A.M., Krenning, E.P. & de Muinck Keizer-Schrama, S.M. Reference data for bone density and body composition measured with dual energy x ray absorptiometry in white children and young adults. *Arch Dis Child* **87**, 341-347; discussion 341-347 (2002).
140. Boot, A.M., Bouquet, J., de Ridder, M.A., Krenning, E.P. & de Muinck Keizer-Schrama, S.M. Determinants of body composition measured by dual-energy X-ray absorptiometry in Dutch children and adolescents. *Am J Clin Nutr* **66**, 232-238 (1997).
141. Maahs, D.M., *et al.* Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. *Circulation* **130**, 1532-1558 (2014).
142. Redondo, M.J., *et al.* Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. *Acta Diabetol* **53**, 271-277 (2016).
143. Minges, K.E., Whittemore, R. & Grey, M. Overweight and obesity in youth with type 1 diabetes. *Annu Rev Nurs Res* **31**, 47-69 (2013).
144. Lipsky, L.M., Gee, B., Liu, A. & Nansel, T.R. Body mass index and adiposity indicators associated with cardiovascular biomarkers in youth with type 1 diabetes followed prospectively. *Pediatr Obes* **12**, 468-476 (2017).

145. Birkebaek, N.H., *et al.* Effect of weight reduction on insulin sensitivity, sex hormone-binding globulin, sex hormones and gonadotrophins in obese children. *Eur J Endocrinol* **163**, 895-900 (2010).
146. Gronbaek, H., *et al.* Effect of a 10-week weight loss camp on fatty liver disease and insulin sensitivity in obese Danish children. *J Pediatr Gastroenterol Nutr* **54**, 223-228 (2012).
147. Gurnani, M., Birken, C. & Hamilton, J. Childhood Obesity: Causes, Consequences, and Management. *Pediatr Clin North Am* **62**, 821-840 (2015).
148. Rankin, J., *et al.* Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. *Adolesc Health Med Ther* **7**, 125-146 (2016).
149. Frohlich-Reiterer, E.E., *et al.* Predictors of increasing BMI during the course of diabetes in children and adolescents with type 1 diabetes: data from the German/Austrian DPV multicentre survey. *Arch Dis Child* **99**, 738-743 (2014).
150. de Vries, L., *et al.* Changes in weight and BMI following the diagnosis of type 1 diabetes in children and adolescents. *Acta Diabetol* **51**, 395-402 (2014).
151. Rawshani, A., *et al.* Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet* **392**, 477-486 (2018).
152. Purnell, J.Q., *et al.* Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial. *JAMA* **280**, 140-146 (1998).
153. Russell-Jones, D. & Khan, R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes Obes Metab* **9**, 799-812 (2007).
154. Conway, B., *et al.* Temporal patterns in overweight and obesity in Type 1 diabetes. *Diabet Med* **27**, 398-404 (2010).
155. Holl, R.W., Grabert, M., Sorgo, W., Heinze, E. & Debatin, K.M. Contributions of age, gender and insulin administration to weight gain in subjects with IDDM. *Diabetologia* **41**, 542-547 (1998).
156. Berg-Kelly, K. *Ungdomars hälsa*, (Studentlitteratur AB, Lund, Sweden, 2014).
157. Clements, M.A., *et al.* Hemoglobin A1c (HbA1c) changes over time among adolescent and young adult participants in the T1D exchange clinic registry. *Pediatr Diabetes* **17**, 327-336 (2016).
158. Kelsey, M.M. & Zeitler, P.S. Insulin Resistance of Puberty. *Curr Diab Rep* **16**, 64 (2016).
159. Rausch, J.R., *et al.* Changes in treatment adherence and glycemic control during the transition to adolescence in type 1 diabetes. *Diabetes Care* **35**, 1219-1224 (2012).
160. King, K.M., King, P.J., Nayar, R. & Wilkes, S. Perceptions of Adolescent Patients of the "Lived Experience" of Type 1 Diabetes. *Diabetes Spectr* **30**, 23-35 (2017).
161. Cameron, F.J., Northam, E.A., Ambler, G.R. & Daneman, D. Routine psychological screening in youth with type 1 diabetes and their parents: a notion whose time has come? *Diabetes Care* **30**, 2716-2724 (2007).
162. Svensson, M., Engstrom, I. & Aman, J. Higher drive for thinness in adolescent males with insulin-dependent diabetes mellitus compared with healthy controls. *Acta Paediatr* **92**, 114-117 (2003).

163. Rydall, A.C., Rodin, G.M., Olmsted, M.P., Devenyi, R.G. & Daneman, D. Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *N Engl J Med* **336**, 1849-1854 (1997).
164. Takii, M.*, et al.* Differences between bulimia nervosa and binge-eating disorder in females with type 1 diabetes: the important role of insulin omission. *J Psychosom Res* **47**, 221-231 (1999).
165. Jones, J.M., Lawson, M.L., Daneman, D., Olmsted, M.P. & Rodin, G. Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study. *BMJ* **320**, 1563-1566 (2000).
166. Neumark-Sztainer, D.*, et al.* Weight control practices and disordered eating behaviors among adolescent females and males with type 1 diabetes: associations with sociodemographics, weight concerns, familial factors, and metabolic outcomes. *Diabetes Care* **25**, 1289-1296 (2002).
167. Garcia-Reyna, N.*, et al.* Eating disorders in 12- to 16-year-old diabetic and nondiabetic adolescents from Barcelona, Spain. *Diabetes Care* **26**, 2695 (2003).
168. Colas, C. Eating disorders and retinal lesions in type 1 (insulin-dependent) diabetic women. *Diabetologia* **34**, 288 (1991).
169. Meltzer, L.J.*, et al.* Disordered eating, body mass, and glycemic control in adolescents with type 1 diabetes. *Diabetes Care* **24**, 678-682 (2001).
170. Engstrom, I.*, et al.* Eating disorders in adolescent girls with insulin-dependent diabetes mellitus: a population-based case-control study. *Acta Paediatr* **88**, 175-180 (1999).
171. Morris, A.D.*, et al.* Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. *Lancet* **350**, 1505-1510 (1997).
172. Peveler, R.C., Fairburn, C.G., Boller, I. & Dunger, D. Eating disorders in adolescents with IDDM. A controlled study. *Diabetes Care* **15**, 1356-1360 (1992).
173. Gregory, J.W.*, et al.* ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes in adolescence. *Pediatr Diabetes* **23**, 857-871 (2022).
174. Graue, M., Wentzel-Larsen, T., Hanestad, B.R. & Sovik, O. Health-related quality of life and metabolic control in adolescents with diabetes: the role of parental care, control, and involvement. *J Pediatr Nurs* **20**, 373-382 (2005).
175. Silverstein, J.*, et al.* Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* **28**, 186-212 (2005).
176. Viklund, G. & Wikblad, K. Teenagers' perceptions of factors affecting decision-making competence in the management of type 1 diabetes. *J Clin Nurs* **18**, 3262-3270 (2009).
177. Karlsson, A., Arman, M. & Wikblad, K. Teenagers with type 1 diabetes--a phenomenological study of the transition towards autonomy in self-management. *Int J Nurs Stud* **45**, 562-570 (2008).
178. Anderson, B.J.*, et al.* Family conflict, adherence, and glycaemic control in youth with short duration Type 1 diabetes. *Diabet Med* **19**, 635-642 (2002).
179. DeBoer, M.D.*, et al.* The Impact of Frequency and Tone of Parent-Youth Communication on Type 1 Diabetes Management. *Diabetes Ther* **8**, 625-636 (2017).

180. Herzer, M., Vesco, A., Ingerski, L.M., Dolan, L.M. & Hood, K.K. Explaining the family conflict-glycemic control link through psychological variables in adolescents with type 1 diabetes. *J Behav Med* **34**, 268-274 (2011).
181. Hilliard, M.E., Wu, Y.P., Rausch, J., Dolan, L.M. & Hood, K.K. Predictors of deteriorations in diabetes management and control in adolescents with type 1 diabetes. *J Adolesc Health* **52**, 28-34 (2013).
182. Hood, K.K., Butler, D.A., Anderson, B.J. & Laffel, L.M. Updated and revised Diabetes Family Conflict Scale. *Diabetes Care* **30**, 1764-1769 (2007).
183. Sand, P., Kleiberg, A.N. & Forsander, G. The reliability and validity of the revised Diabetes Family Conflict Scale questionnaire, in a sample of Swedish children. *Acta Paediatr* **102**, 650-654 (2013).
184. Ingerski, L.M., Anderson, B.J., Dolan, L.M. & Hood, K.K. Blood glucose monitoring and glycemic control in adolescence: contribution of diabetes-specific responsibility and family conflict. *J Adolesc Health* **47**, 191-197 (2010).
185. Cameron, F.J.*, et al.* Are family factors universally related to metabolic outcomes in adolescents with Type 1 diabetes? *Diabet Med* **25**, 463-468 (2008).
186. Lindstrom, C., Aman, J., Norberg, A.L., Forssberg, M. & Anderzen-Carlsson, A. "Mission Impossible"; the Mothering of a Child With Type 1 Diabetes - From the Perspective of Mothers Experiencing Burnout. *J Pediatr Nurs* **36**, 149-156 (2017).
187. Shorer, M.*, et al.* Role of parenting style in achieving metabolic control in adolescents with type 1 diabetes. *Diabetes Care* **34**, 1735-1737 (2011).
188. Goethals, E.R.*, et al.* Communication matters: The role of autonomy-supportive communication by health care providers and parents in adolescents with type 1 diabetes. *Diabetes Res Clin Pract* **163**, 108153 (2020).
189. Franceschi, R.*, et al.* Impact of intermittently scanned continuous glucose monitoring with alarms on sleep and metabolic outcomes in children and adolescents with type 1 diabetes. *Acta Diabetol* **59**, 911-919 (2022).
190. Howe, C.J., Ayala, J., Dumser, S., Buzby, M. & Murphy, K. Parental expectations in the care of their children and adolescents with diabetes. *J Pediatr Nurs* **27**, 119-126 (2012).
191. Datye, K.A., Moore, D.J., Russell, W.E. & Jaser, S.S. A review of adolescent adherence in type 1 diabetes and the untapped potential of diabetes providers to improve outcomes. *Curr Diab Rep* **15**, 51 (2015).
192. Sveriges kommuner och regioner (SKR) Nationella Kvalitetsregister. Vol. 2025 (2025).
193. Wettermark, B.*, et al.* The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* **16**, 726-735 (2007).
194. Lindblad, B. & Nordin, G. External quality assessment of HbA1c and its effect on comparison between Swedish pediatric diabetes clinics. Experiences from the Swedish pediatric diabetes quality register (Swediabkids) and Equalis. *Clin Chem Lab Med* **51**, 2045-2052 (2013).
195. National Glycohemoglobin Standardization Program (NGSP). Vol. 2022.
196. Tjora, A. *Från nyfikenhet till systematisk kunskap-kvalitativ forskning i praktiken*, (Studentlitteratur, Lund, 2012).
197. Bryman, A. *Social research methods*, (Oxford University Press, Oxford ; New York, 2016).

198. Graneheim, U.H. & Lundman, B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* **24**, 105-112 (2004).
199. Statistics Sweden (SCB).
200. The County Östersund. (2025).
201. The County Umeå. (2024).
202. Graneheim, U.H., Lindgren, B.M. & Lundman, B. Methodological challenges in qualitative content analysis: A discussion paper. *Nurse Educ Today* **56**, 29-34 (2017).
203. Lindgren, B.M., Lundman, B. & Graneheim, U.H. Abstraction and interpretation during the qualitative content analysis process. *Int J Nurs Stud* **108**, 103632 (2020).
204. Pankowska, E., Blazik, M., Dziechciarz, P., Szypowska, A. & Szajewska, H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr Diabetes* **10**, 52-58 (2009).
205. Blair, J.C.*, et al.* Continuous subcutaneous insulin infusion versus multiple daily injection regimens in children and young people at diagnosis of type 1 diabetes: pragmatic randomised controlled trial and economic evaluation. *BMJ* **365**, l1226 (2019).
206. Olsen, B.*, et al.* Insulin pump treatment; increasing prevalence, and predictors for better metabolic outcome in Danish children and adolescents with type 1 diabetes. *Pediatr Diabetes* **16**, 256-262 (2015).
207. Konrad, K.*, et al.* Current practice of diabetes education in children and adolescents with type 1 diabetes in Germany and Austria: analysis based on the German/Austrian DPV database. *Pediatr Diabetes* **17**, 483-491 (2016).
208. Toresson Grip, E.*, et al.* Real-World Costs of Continuous Insulin Pump Therapy and Multiple Daily Injections for Type 1 Diabetes: A Population-Based and Propensity-Matched Cohort From the Swedish National Diabetes Register. *Diabetes Care* **42**, 545-552 (2019).
209. Ibfelt, E.H.*, et al.* Association between glycaemic outcome and BMI in Danish children with type 1 diabetes in 2000-2018: a nationwide population-based study. *Diabet Med* **38**, e14401 (2021).
210. Birkebaek, N.H.*, et al.* Body mass index standard deviation score and obesity in children with type 1 diabetes in the Nordic countries. HbA(1c) and other predictors of increasing BMISDS. *Pediatr Diabetes* **19**, 1198-1205 (2018).
211. Ludvigsson, J. & Samuelsson, U. Continuous insulin infusion (CSII) or modern type of multiple daily injections (MDI) in diabetic children and adolescents a critical review on a controversial issue. *Pediatr Endocrinol Rev* **5**, 666-678 (2007).
212. Seget, S.*, et al.* Body mass index, basal insulin and glycemic control in children with type 1 diabetes treated with the advanced hybrid closed loop system remain stable - 1-year prospective, observational, two-center study. *Front Endocrinol (Lausanne)* **13**, 1036808 (2022).
213. Piccini, B.*, et al.* Glycemic Control, Basal/Bolus Distribution, BMI and Meal Management in Children and Adolescents with Type 1 Diabetes and Advanced Hybrid Closed Loop. *Nutrients* **15**(2023).

214. Sherr, J.L.*, et al.* Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. *Diabetologia* **59**, 87-91 (2016).
215. Pickup, J.C. & Sutton, A.J. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* **25**, 765-774 (2008).
216. Jeitler, K.*, et al.* Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* **51**, 941-951 (2008).
217. Zimmermann, A.T.*, et al.* Treatment regimens and glycaemic outcomes in more than 100 000 children with type 1 diabetes (2013-22): a longitudinal analysis of data from paediatric diabetes registries. *Lancet Diabetes Endocrinol* **13**, 47-56 (2025).
218. Zabeen, B.*, et al.* Insulin Pump Therapy Is Associated with Lower Rates of Retinopathy and Peripheral Nerve Abnormality. *PLoS One* **11**, e0153033 (2016).
219. Biester, T.*, et al.* International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2024: Diabetes Technologies - Insulin Delivery. *Horm Res Paediatr* **97**, 636-662 (2024).
220. Maiorino, M.I.*, et al.* Effects of Continuous Glucose Monitoring on Metrics of Glycemic Control in Diabetes: A Systematic Review With Meta-analysis of Randomized Controlled Trials. *Diabetes Care* **43**, 1146-1156 (2020).
221. Bergenstal, R.M.*, et al.* Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* **363**, 311-320 (2010).
222. Battelino, T.*, et al.* Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* **34**, 795-800 (2011).
223. Beck, R.W.*, et al.* Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. *JAMA* **317**, 371-378 (2017).
224. El-Laboudi, A.H., Godsland, I.F., Johnston, D.G. & Oliver, N.S. Measures of Glycemic Variability in Type 1 Diabetes and the Effect of Real-Time Continuous Glucose Monitoring. *Diabetes Technol Ther* **18**, 806-812 (2016).
225. Dicembrini, I., Cosentino, C., Monami, M., Mannucci, E. & Pala, L. Effects of real-time continuous glucose monitoring in type 1 diabetes: a meta-analysis of randomized controlled trials. *Acta Diabetol* **58**, 401-410 (2021).
226. Karges, B.*, et al.* Continuous glucose monitoring versus blood glucose monitoring for risk of severe hypoglycaemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: a population-based study. *Lancet Diabetes Endocrinol* **11**, 314-323 (2023).
227. Sundberg, F., Natman, J., Franzen, S., Akesson, K. & Sarnblad, S. A decade of improved glycemic control in young children with type 1 diabetes: A population-based cohort study. *Pediatr Diabetes* **22**, 742-748 (2021).
228. Sumnik, Z.*, et al.* Glycemic Control by Treatment Modalities: National Registry-Based Population Data in Children and Adolescents with Type 1 Diabetes. *Horm Res Paediatr* **97**, 70-79 (2024).
229. Boughton, C.K.*, et al.* Closed-Loop Therapy and Preservation of C-Peptide Secretion in Type 1 Diabetes. *N Engl J Med* **387**, 882-893 (2022).

230. Sochett, E.B., Daneman, D., Clarson, C. & Ehrlich, R.M. Factors affecting and patterns of residual insulin secretion during the first year of type 1 (insulin-dependent) diabetes mellitus in children. *Diabetologia* **30**, 453-459 (1987).
231. Gronberg, A., Espes, D., Carlsson, P.O. & Ludvigsson, J. Higher risk of severe hypoglycemia in children and adolescents with a rapid loss of C-peptide during the first 6 years after type 1 diabetes diagnosis. *BMJ Open Diabetes Res Care* **10**(2022).
232. de Vries, S.A.G., Verheugt, C.L., Mul, D., Nieuwdorp, M. & Sas, T.C.J. Do sex differences in paediatric type 1 diabetes care exist? A systematic review. *Diabetologia* **66**, 618-630 (2023).
233. Sassmann, H.*, et al.* Understanding Daily, Emotional, and Physical Burdens and Needs of Parents Caring for Children with Type 1 Diabetes. *J Diabetes Res* **2022**, 9604115 (2022).
234. Fremont, E.R. & Miller, V.A. Perspectives on Remote Glucose Monitoring in Youth With Type 1 Diabetes. *J Pediatr Psychol* **46**, 1276-1285 (2021).
235. Bisio, A.*, et al.* Sleep and diabetes-specific psycho-behavioral outcomes of a new automated insulin delivery system in young children with type 1 diabetes and their parents. *Pediatr Diabetes* **22**, 495-502 (2021).
236. Boucher, S.E.*, et al.* Exploring parental perspectives after commencement of flash glucose monitoring for type 1 diabetes in adolescents and young adults not meeting glycaemic targets: a qualitative study. *Diabet Med* **37**, 657-664 (2020).
237. Cobry, E.C.*, et al.* Health-Related Quality of Life and Treatment Satisfaction in Parents and Children with Type 1 Diabetes Using Closed-Loop Control. *Diabetes Technol Ther* **23**, 401-409 (2021).
238. Kulzer, B., Heinemann, L. & Roos, T. Patients' Experience of New Technologies and Digitalization in Diabetes Care in Germany. *J Diabetes Sci Technol* **16**, 1521-1531 (2022).
239. NDR-SWEDIABKIDS. Swedish National Quality Registry for Diabetes in Children and Adolescents. Vol. 2022 (2021).
240. Peterson, A.*, et al.* Improved results in paediatric diabetes care using a quality registry in an improvement collaborative: a case study in Sweden. *PLoS One* **9**, e97875 (2014).
241. Samuelsson, U., Akesson, K., Peterson, A., Hanas, R. & Hanberger, L. Continued improvement of metabolic control in Swedish pediatric diabetes care. *Pediatr Diabetes* **19**, 150-157 (2018).
242. Recommendations for the usage of continuous glucose monitoring in Swedish children and adolescents with type 1 diabetes. (2017).
243. Jespersen, L.N., Svensson, J., Pilgaard, K.A. & Grabowski, D. Communication and Social Relations: A Qualitative Study of Families' Experience with Their Outpatient Pediatric Diabetes Visits. *Children (Basel)* **9**(2022).