

The choice of insulin regimen and target of glycemic control in children with type 1 diabetes mellitus

-A comparative study of Canada and Norway



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Student thesis at the Faculty of Medicine
University of Oslo
Norway

November 2011

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-A comparative study of Canada and Norway

1. Acknowledgements

This student thesis was carried out in the years between 2009 and 2011 while we were medical students at the Faculty of Medicine at the University of Oslo, Norway.

First of all we want to thank our supervisors; senior consultant Torild Skrivarhaug MD PhD and professor Borghild Roald MD PhD at Oslo University Hospital (OUS), Norway. Torild has taught us about type 1 diabetes mellitus (T1DM) in children and Borghild has helped us focus on the global perspective of childhood diabetes. They have both encouraged and supported us in our work and given us valuable advice and aided in designing and evaluating the questionnaire. They have read through our thesis several times and given us constructive feedback.

During the spring of 2009 we made a questionnaire aimed at making a survey on diabetes in children and adolescents together with our fellow student colleagues Idun Stenhammer Aanerød, Lise Haldorsen Willumsen, Martine Aurora Munkvold and Lene Sleire. We thank diabetes nurse Siv Janne Kummernes at OUS for giving us valuable help in adjusting our questionnaire and completing the Norwegian data. We thank Haneef Awan who made an electronic version of the questionnaire.

During the summer of 2010 we travelled to Canada together with our fellow student Lene Sleire who also participated in the interviews we did at the British Columbia Children's Hospital (BCCH), Vancouver, British Columbia and The Hospital for Sick Children (SickKids), Toronto, Ontario.

We thank Dr Daniel Metzger at the BCCH who kindly gave his time to answer the questions in the questionnaire and let us interview him. We are grateful for the opportunity to sit in with, observing and discussing with the different members of the diabetes team at the diabetes outpatient clinic.

We thank Dr Denis Daneman at SickKids for letting us visit him and for helping us find the answers in our questionnaire. We also thank the friendly staff and different members of the diabetes team at the outpatient clinic at SickKids who took the time to letting us interview them.

Oslo, November 2011

Natalie Lie Berntsen and Eirin Eilertsen

2. Abbreviations

AC	Albumin Concentration
ACR	Albumine Creatinin Ratio
ADA	American Diabetes Association
AER	Albumin Excretion Rate
BCCH	British Columbia Children's Hospital
BG	Blood Glucose
CDA	Canadian Diabetes Association
CNS	Central Nervous System
CPG	Clinical Practice Guidelines
CSGM	Continous Subcutaneous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
DDP	Diabetes Day Program
DiaMond	The Diabetes Mondiale study
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DSME	Diabetes Self-Management Education
EURODIAB	The Europe and Diabetes Study
ESRD	End-Stage Renal Disease
FPG	Fasting Plasma Glucose
GAD	Glutamic Acid Decarboxylase
HbA1c	Glycated Hemoglobin
HLA	Human Leukocyte Antigen
IAAs	Autoantibodies to Insulin
IA2 and IA-2 β	Autoantibodies to the tyrosine phosphatises
ICAs	Islet cell autoantibodies
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
ISPAD	International Society for Pediatric and Adolescent Diabetes
MDI	Multiple Daily Injections
MODY	Maturity Onset Diabetes of the Young
NCDR	Norwegian Childhood Diabetes Registry
NDP	National Diabetes Programs
NICE	National Institute for health and Clinical Excellence
NPH	Neutral Protamine Hagedorn
OGTT	Oral Glucose Tolerance Test
OUS	Oslo University Hospital
RCT	Randomized Controlled Trial
SickKids	Hospital for Sick Children
SMBG	Self-Monitoring of Blood Glucose
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization

3. Abstract

Background

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia. Type 1 diabetes mellitus (T1DM) is one of the most common endocrine and metabolic conditions in childhood, rapidly increasing in incidence and associated with increased long-term morbidity and mortality. Optimal diabetes management to avoid or delay the long-term complications of diabetes is important. Diabetes education remains a cornerstone in this work, in addition to optimal diabetes treatment, glycemic control and avoidance of the short-term complications of diabetes while screening for complications and the associated comorbidities.

Aims

The aim of this thesis is a comparative study of Norway and Canada, focusing on the choice of target of glycemic control and insulin regimen in treatment of T1DM in children.

Methods

This thesis consists of two parts; Part one is a literature review on T1DM based upon a non-systematic search in PubMed. Part two is the clinical part of our thesis. We made an electronic questionnaire based on international guidelines and performed a combined survey and interviews in addition to our clinical experiences visiting hospitals in Norway (Oslo University Hospital (OUS)) and Canada (British Columbia Childrens's Hospital (BCCH) and Hospital for Sick Children (SickKids)).

Results

Performing our comparative study of Norway and Canada we found that management of childhood T1DM had many similarities in terms of diabetes management, e.g. diabetes education and composition of the multidisciplinary team. Some differences between the nations and hospitals exist in guidelines, management at the time of diagnosis, hospital admittance, frequency of follow up, choice of insulin regimen and target of glycemic control. While every child diagnosed with T1DM at OUS is offered to start with an insulin pump at diagnosis, all the children at SickKids are started on insulin injection therapy. The two Canadian hospitals both preferred to wait with pump therapy. Approximately two thirds of the Canadian patients were on conventional regimens, compared to almost none at OUS. Both Canadian Hospitals had age-adjusted HbA1c targets that were higher than OUS for the children less than 12 years of age.

Conclusion

Optimal diabetes management to avoid short- and long-term complications is important. Children with T1DM should, where possible, receive the best diabetes care available. The hospitals we visited in Norway and Canada all had well-organized diabetes care, mostly according to international guidelines of pediatric diabetes. Tight glycemic control and intensive insulin regimen has been shown to reduce and delay the diabetes late complications and should be included as part of the management of childhood diabetes.

4. Aims and methods

4.1. Aims

Our student thesis is part of a larger study with six fellow medical students; “Diabetes in children; a global, comparative study”. The aim of this study is a survey of how children with diabetes are diagnosed, treated and followed up throughout the world based upon clinical experiences and by carrying out combined surveys and interviews. Our group of students has travelled to various countries in the world including the United States, Australia, Canada, Rwanda and India. We aim at identifying the national, regional or local modifications to international guidelines of pediatric diabetes that are made throughout the world. We also wanted to focus upon challenges, obstacles and restraints in the various countries visited and the ways they are met.

The aim of this thesis was a comparative study between Norway and Canada. We focus primarily on T1DM, as this is the most common type of diabetes in children, especially in the western world. We have concentrated on the choice of target of glycemic control and insulin regimen in treatment of diabetes in Canada and Norway, the influence of hypoglycemia and the importance of diabetes education, diabetes multidisciplinary teams and the follow-up with regard to these themes.

4.2. Methods

This student thesis consists of two parts; Part one is a literature review on T1DM and part two is the clinical survey. Most of our sources of information derive from a non-systematic search in PubMed and from the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines references.

Performing a global, comparative study, all the students that are part of our larger study decided to do a combined survey and interviews in addition to our clinical experiences. Travelling to different parts of the world, we have used the same questionnaire so that our data will be more easily comparable.

During the spring of 2009 we made an electronic questionnaire (appendix 1) based on the 2009 ISPAD and American Diabetes Association (ADA) guidelines together with four of our fellow students at the University of Oslo; Lene Sleire, Martine Aurora Munkvold, Lise Haldorsen Willumsen and Idun Stenhammer Aanerød. This work was done with the help of prof. Borghild Roald and senior consultant Torild Skrivarhaug, who evaluated and gave us feedback on our questionnaire and diabetes nurse Siv Janne Kummernes at the OUS, pediatric department who gave an interview and helped us adjust our questionnaire. The questionnaire was our tool in the semistructured interviews of health workers in Norway and Canada to gather information on T1DM in children and adolescents. It consists of two parts; the first part concerns information regarding incidence, prevalence, mortality, national health, patient organizations, registers and complications in the state/country we were studying. The second part focuses on the single hospitals/departments, e.g.

hospitalizations, diagnostics, treatment and follow up, treatment goals and quality of life and mental health.

Part two of our thesis is based upon our experiences and the information we gathered interviewing health workers during our visits to three different hospitals in Norway and Canada during the time between May and July 2010. We visited OUS, Ullevål in Oslo, Norway. In Canada we visited BCCH in Vancouver, British Columbia and SickKids in Toronto, Ontario. At OUS we interviewed diabetes nurse Kummernes, attended diabetes clinics and sat in with our supervisor Dr. Torild Skrivarhaug at her clinics. At BCCH we interviewed Dr. Daniel Metzger and sat in with different members of the diabetes team at the diabetes clinic. We also visited a primary health care center specializing in diabetes management and education in Vancouver. At SickKids we interviewed Dr. Denis Daneman and different members of the diabetes team at the diabetes clinic.

The questionnaire was sent to the interview subjects via e-mail in advance of the interview. The interviews were tape recorded, and transcribed shortly after the interviews. The information gathered from these interviews contains no sensitive patient information. Parts of the information we gathered to complete the questionnaire was found in literature and from the Internet.

5. PART ONE

- Literature review on T1DM in children and adolescents

5.1.Introduction- diabetes mellitus

DM is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both (1). T1DM is one of the most common endocrine and metabolic conditions in childhood and is rapidly increasing in many countries, especially amongst the youngest children. In 2010, the total child population of the world (0 – 14 years) was estimated to be 1.9 billion, of whom 0.025% has diabetes. This means that approximately 480,000 children around the world have diabetes with 75,800 new cases diagnosed each year and an annual increase in 3,0% (2).

Insulin treatment is life-saving and lifelong. Self-discipline and adherence to a balanced diet is necessary to manage T1DM. In many countries, especially in less privileged families, access to self-care tools and insulin is limited. This may lead to severe handicap and early death in patients with T1DM.

From a global perspective, lack of insulin is the most common cause of death in a child with T1DM. Many children die before their diabetes is diagnosed (3). Establishing an international collaboration to decrease morbidity and mortality in children with T1DM is important. The International Diabetes Federation (IDF) "Life for a Child" program was established in 2001 with support from the Australian Diabetes Council and the international charity *HOPE worldwide*. "Life for a child" is a support program in collaboration with ISPAD and other organizations in which

individuals, families and organizations contribute to help children with diabetes in developing countries (4).

The ISPAD guidelines 2009 places diabetes education at the center of clinical management; “Education is the vehicle for optimal self-management, the key to success” (2).

5.1.1. History

T1DM was once a fatal disease. After the onset of clinical symptoms patients would usually die within a year or two. The discovery of insulin at the University of Toronto, Canada in 1922 revolutionized the treatment and prognosis of the disease. Dr. Frederick Banting and biochemist J.J.R. Macleod, both Canadians, were in 1923 awarded the Nobel Prize in Medicine for the discovery of insulin. Dr. Banting shared his prize with his laboratory assistant, Charles Best, and MacLeod shared his with biochemist James Collip. The patent for insulin was sold to the University of Toronto for one half Canadian dollar (5).

Before the age of genetics, the only insulin available was purified animal-sourced insulin, mostly made from pigs or cattle. The amino-acid structure of insulin was discovered in the 1950’s, and in the early 1960’s the first synthetic insulin was produced. In 1977 Herbert Boyer made the first genetically-engineered synthetic “human” insulin, using E.coli. Boyer and Eli Lilly and Company offered the first commercially available human insulin – Humulin on the market. Today most insulin used still are recombinant human insulin or its analogues (6).



Fig. 1. The Flame of Hope, London, Ontario (36)

Canada was the country in which insulin was first used to treat diabetes and the country still has high ambitions on behalf of diabetes treatment. Researchers are working to improve the quality of life for people with diabetes, as well as working to find a cure for the disease. The *Flame of Hope* (front page and Fig.1) is a flame that was lit at Sir Fredrick Banting Square in London, Ontario in 1989 as a tribute to Dr. Banting and all the people that have lost their lives to diabetes. The flame will remain lit until there is a cure for diabetes (7).

5.1.2. Classification of DM

DM is traditionally classified into two main types; T1DM and type 2 diabetes mellitus (T2DM). Some other subtypes exist. The ADA and an expert committee from the World Health Organization (WHO) recommend an etiological taxonomy on the classification and diagnosis of diabetes (1):

Etiological classification of disorders of glycemia	
I. Type 1 diabetes mellitus (T1DM)	β -cell destruction, usually leading to absolute insulin deficiency
A. Immune mediated	
B. Idiopathic	
II. Type 2 diabetes mellitus (T2DM)	May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance
III. Other specific types	
A. Genetic defects of β -cell function	
B. Genetic defects in insulin action	
C. Diseases of the exocrine pancreas	
D. Endocrinopathies	
E. Drug- or chemical-induced	
F. Infections	
G. Uncommon forms of immune-mediated diabetes	
H. Other genetic syndromes sometimes associated with diabetes	
IV. Gestational diabetes	

Table 1. Etiological classification of disorders of glycemia (1)

Classifying DM into T1DM, T2DM and monogenic diabetes has important implications for both therapeutic decisions and educational approaches, even though the child presenting with severe fasting hyperglycemia will require insulin therapy regardless of the type. In most western countries T1DM accounts for more than 90% of childhood and adolescent diabetes, but T2DM is becoming more common and accounts for a significant proportion of DM in certain at risk populations (8). The possibility of other types of diabetes should be considered when suspected, e.g. with an autosomal dominant family history of diabetes, associated conditions or syndromic features in the child or a history of exposure to drugs known to be toxic to beta cells or cause insulin resistance. Characteristic features of T1DM in comparison with T2DM and monogenic diabetes in children and adolescents are shown in table 2 (1).

Characteristic	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often post pubertal except Glucokinase and neonatal diabetes
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in glucokinase)
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in neonatal diabetes, rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% Japan 60-80%	?1-3%
Parent with diabetes	2-4%	80%	90%

Table 2. Clinical characteristics of type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and monogenic diabetes mellitus (DM) in children and adolescents (1)

5.1.3. Etiology and pathogenesis

T1DM has a prodromal phase in with a progressive loss of insulin-producing beta-cells in the Langerhans islets in the pancreas. By the time of diagnosis, only 10-20 % of insulin-producing beta-cells are still functioning (9). In most cases T1DM has an autoimmune pathogenesis with autoantibodies to glutamic acid decarboxylase (GAD), islet cell autoantibodies (ICAs) and/or insulin autoantibodies (IAAs). These serological markers of an underlying autoimmune process can be found circulating in the blood at the time of diagnosis in 85-90 % of patients (9).

Several theories have been proposed on the etiology and pathogenesis of DM. Eisenbarth proposed our current model for T1DM, subtype A in the 1980s. This theory claims that we are all born with a certain degree of genetic susceptibility for T1DM, decided in our Human Leukocyte Antigen (HLA) genotypes DR and DQ and to a lesser extent in a host of other genetic loci called insulin-dependent diabetes mellitus (IDDM) susceptibility genes. HLA locus counts for about 50 % of the genetic susceptibility (10).

Genetic susceptibility is not enough for developing T1DM. In monozygotic twins where one of the twins has T1DM, the other twin will develop the disease only in about 36% (10). Contributing factors to developing T1DM has been hypothesized, but not verified (1, 10, 11):

- Viruses (enteroviruses, coxsackie, congenital rubella)
- Environmental toxins (nitrosamines)
- Foods (gluten, cereals, early exposure to cow's milk proteins)
- Vitamin D deficiency
- Perinatal factors (maternal age, preeclampsia and neonatal jaundice)

5.1.4. Epidemiology

5.1.4.1. World epidemiology

Many countries in the world keep records of the incidence of T1DM. The International Diabetes Federation (IDF) collects data on diabetes worldwide and published its first Diabetes Atlas in 2000 showing the incidence of T1DM around the world (12).

Two international collaborative projects; the Diabetes Mondiale study (DiaMond) and the Europe and Diabetes study (EURODIAB) began monitoring trends in incidence in the 1980s. The data has been collected through the establishment of population-based regional or national registries using standardized definitions, data collection forms and methods for validation (3).

The incidence of T1DM varies greatly between different countries, within countries and between different ethnic populations. Finland and Sardinia are among the countries with the highest incidences (37 to 57,6 per 100 000 children 0-14 years of age). Venezuela and parts of China have the lowest incidence (0,1 to 0,5 per 100 000) (11,12). Countries with high latitudes tend to have a higher incidence (11). An annual

increase in the incidence of T1DM by 2-5 % each year is reported in Europe, The Middle East and Australia (11). There is also a tendency of a more steep increase in some of the low prevalence countries in Central and Eastern Europe (3).

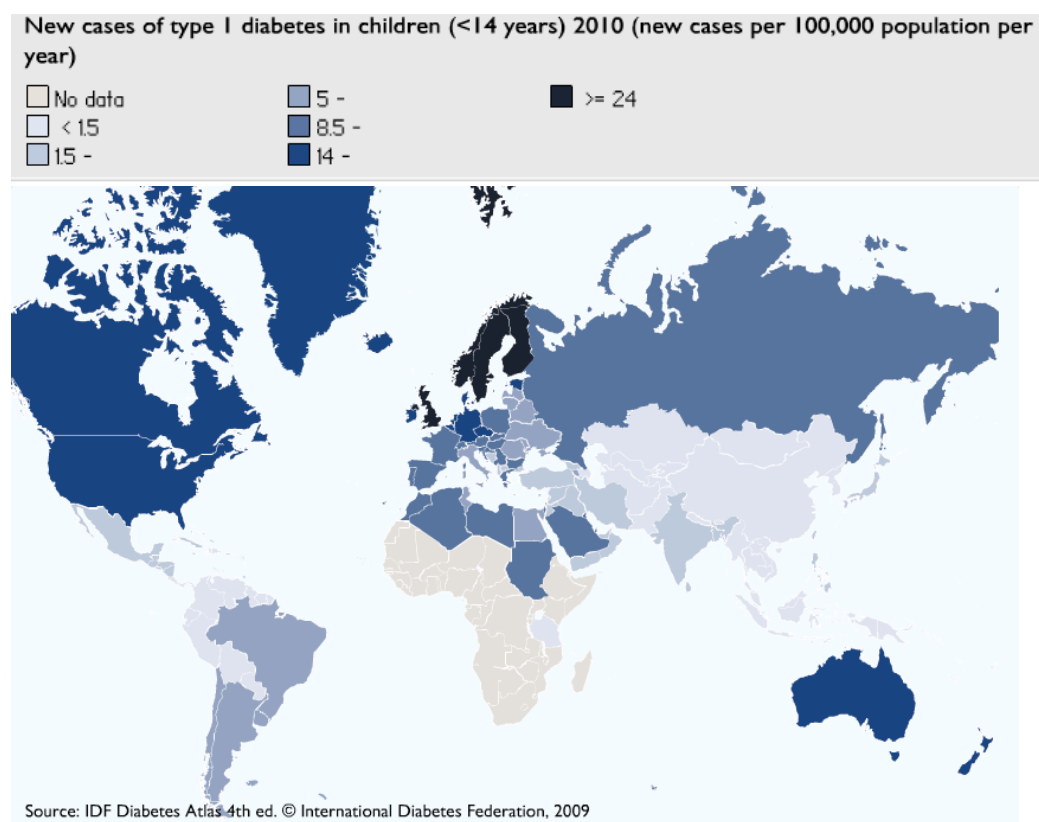


Fig. 2. New cases of type 1 diabetes mellitus (T1DM) in children 2010 (13).

5.1.4.2. Norway

The incidence of T1DM in children 0-14 years of age in Norway is about 36 per 100 000 per year (14). Norway has also witnessed an increasing incidence, about 1-3 % every year, with the greatest increase in the age group 10-14 years of age (15). In 2009, 335 new cases of T1DM in children 0-15 years were reported to the Norwegian Childhood Diabetes Registry (NCDR). More than 95 % of cases in this age group had T1DM (14). In the EURODIAB study, Norway had the fifth highest incidence rate (1989-1998) in Europe (16).

5.1.4.3. Canada

In 2010 Canada had an incidence of about 22 per 100 000 per year of T1DM in children 0-14 years of age (17). This is the sixth highest incidence rate of T1DM in children 0-14 years of age in the world. The incidence rate is rising 3-5 % in Canada, with the greatest increase in the age group 5-9 years (17). The incidence of T1DM varies within Canada. Two areas – the Prince Edwards Islands at the west coast and Newfoundland have an incidence of more than 40 per 100 000 per year of T1DM. Different ethnic groups has different incidence of T1DM (18).

5.1.5. Clinical guidelines

The way health professionals care for children with T1DM can vary between different regions within one country as well as between different countries. T1DM is a lifelong disease associated with increased morbidity and reduced quality of life, especially in individuals with late complications. It is considered important to optimize diabetes care in order to prevent or delay the development of late complications.

Implementation of guidelines to help optimize diabetes care will benefit the individual patient and his or her family as well as the health care system and the society. Late complications of diabetes lead to increased costs for both the patient and the society and the cost-benefit of interventions to improve diabetes care has been well established by several studies (19). The IDF has published a “Guide for Guidelines” as a help to establish realistic guidelines in their country or organization.

5.1.5.1. International Society for Pediatric and Adolescent Diabetes (ISPAD)

ISPAD was established in 1974 and presents itself as a professional international organization whose aims are to promote clinical and basic research, education and advocacy in childhood and adolescent diabetes. The strength of ISPAD lies in the scientific and clinical expertise of its members. ISPAD is the only international society focusing specifically on all types of childhood diabetes and publishes the journal *Pediatric Diabetes* (12).

In 1993 ISPAD formulated the *Declaration of Kos*, intended to proclaim their commitment to “promote optimal health, social welfare and quality of life for all children with diabetes around the world by the year 2000”. The first set of ISPAD consensus guidelines was published in 1995, the second set in 2000. These guidelines have contributed to increased knowledge of childhood and adolescent diabetes worldwide. The ISPAD guidelines have been translated into 11 different languages. The current edition, the *ISPAD Clinical Practice Consensus Guidelines 2009 Compendium*, was published in 2009 (2). Norway adheres to the ISPAD Guidelines for childhood and adolescent diabetes.

5.1.5.2. Canadian Diabetes Association (CDA)

The CDA was founded in 1953 and is active in more than 150 Canadian communities. CDAs slogan says; “We’re leading the fight against diabetes by helping people with diabetes live healthy lives while working to find a cure”. In 2008 CDA published the *Canadian Diabetes Association 2008 Clinical Practice Guidelines (CDA CPG) for the Prevention and Management of Diabetes in Canada* (20). These current guidelines are for the most part aimed at the adult diabetic population, but they include two chapters on T1DM and T2DM in children and adolescents.

These guidelines recognize that the most effective treatment is not necessarily the most cost-effective ones when it comes to social economics (20).

5.1.6. Diagnostic criteria

Symptoms of diabetes are often the classical triade of polyuria, polydipsia and unexplained weight loss (1, 20).

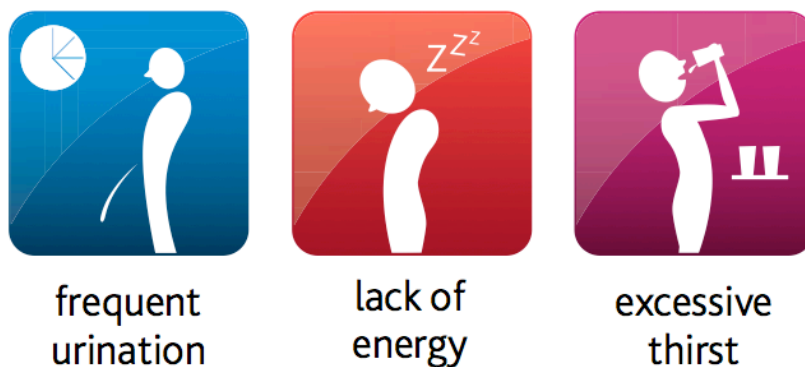


Fig.3. The warning signs of diabetes (21).

The diagnosis of T1DM is based on measurements of blood glucose and clinical symptoms.

ISPAD and CDA criteria for the diagnosis of diabetes mellitus.
1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 11.1 mmol/L OR
2. Fasting plasma glucose (FPG) ≥ 7.0 mmol/l OR
3. 2-hour postload glucose ≥ 11.1 mmol/l during an oral glucose tolerance test (OGTT)

Table 3. International Society for Pediatric and Adolescent Diabetes (ISPAD) and Canadian Diabetes Association (CDA) criteria for the diagnosis of diabetes mellitus. Casual is defined as any time of day without regard to time since last meal. Fasting is defined as no caloric intake for at least 8 hours (1,20).

5.1.7. Education and multidisciplinary team

5.1.7.1. Education

Both the ISPAD guidelines and the CDA CPG emphasize the importance of a multidisciplinary pediatric diabetes healthcare team in the education of children with newly diagnosed T1DM and their families. "Education is the keystone of diabetes care and structured self-management education is the key to a successful outcome" (22).

The CDA CPG states that education topics should include:

- Insulin action, administration and dosage adjustment
- Blood glucose (BG) and ketone testing
- Sick-day management
- Prevention of diabetic ketoacidosis (DKA)
- Nutritional therapy
- Exercise
- Prevention, detection, and treatment of hypoglycemia

Extra attention should be given special events such as school entry, high school entry etc. (20).

ISPAD suggestions include dividing education into primary and secondary levels with basic survival skills at diagnosis, and a continuing curriculum as the child grows older and time goes by:

<p>Primary (level 1) education At diagnosis: Survival skills</p> <ol style="list-style-type: none">1. Explanation of how the diagnosis has been made and reasons for symptoms2. Simple explanation of the uncertain cause of diabetes. No cause for blame3. The need for immediate insulin and how it will work4. What is glucose? - normal BG levels and glucose targets5. Practical skills - insulin injections - blood and/or urine testing and reasons for monitoring6. Basic dietetic advice7. Simple explanation of hypoglycemia8. Diabetes during illnesses. Advice not to omit insulin—prevent DKA9. Diabetes at home or at school including the effects of exercise10. Identity cards, necklets, bracelets and other equipment11. Membership of a Diabetes Association and other available support services12. Psychological adjustment to the diagnosis13. Details of emergency telephone contacts. <p>Secondary (level 2) education Continuing educational curriculum</p> <ol style="list-style-type: none">1. Pathophysiology, epidemiology, classification and metabolism2. Insulin secretion, action and physiology3. Insulin injections, types, absorption, action profiles, variability and adjustments4. Nutrition—food plans; qualitative and quantitative advice on intake of carbohydrate, fat, proteins and fiber; coping with special events and eating out; growth and weight gain; “diabetic foods”; sweeteners and drinks5. Monitoring, including glycated hemoglobin and clear (agreed) targets of control6. Hypoglycemia and its prevention, recognition and management including glucagon7. Intercurrent illness, hyperglycemia, ketosis and prevention of ketoacidosis8. Problem solving and adjustments to treatment9. Goal setting10. Micro and macro-vascular complications and their prevention. The need for regular assessment11. Exercise, holiday planning and travel, including educational holidays and camps12. Smoking, alcohol and drugs13. School, college, employment and driving vehicles14. Sexuality, contraception, pregnancy and childbirth15. Updates on research.
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Table 4. International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendations on organization of diabetes education (22)

Different ways of making diabetes knowledge more accessible for the children with diabetes and their caregivers can be:

- Distribution of written material i.e. written guidelines and booklets
- Using an appropriate language
- Using multimedia tools e.g. videos, CDs and computer games
- Attending diabetes camps, where the children and families can increase their knowledge about diabetes and meet with other children with diabetes and families that are in the same situation.

ISPAD Guidelines emphasize some universal principles for diabetes education. Its characteristics should be (22):

- Easily accessible
- Delivered by healthcare professionals who have an understanding of the special and changing needs of young people as they go through different stages of life,
- Adaptable and personalized,
- Based on thorough assessment of the person's attitudes, beliefs, learning style, ability and readiness to learn, existing knowledge and goals.
- Educators should have access to continuing specialized training in diabetes education and educational methods,
- Part of a continuous process and repeated for it to be effective.

5.1.7.2. Diabetes multidisciplinary team

Dr. Elliot Joslin (1869-1962) was the first American diabetes specialist. He was a pioneer in the field of teaching patients to care for their own disease, a concept now known as diabetes self-management education (DSME). Dr. Joslin thought it important to have multiple health care professionals participating in the treatment of people with diabetes and he began developing the concept of the diabetes team. He is accredited of having said: “the diabetic who knows the most lives the longest” (23).

A multidisciplinary team providing diabetes care should as a minimum consist of a diabetes specialist nurse and a dietician. ISPAD recommend that it consists of:

- Pediatrician specializing in diabetes or endocrinology (or physician with a special interest in childhood and adolescent diabetes)
- Diabetes nurse specialist or diabetes nurse educator
- Dietitian (or nutritionist)
- Pediatric social worker with training in childhood diabetes and chronic illness and/or psychologist trained in pediatrics and with knowledge of childhood diabetes and chronic illness
- The family and child should be recognized as part of the team

It is recognized that in geographical areas with a low population density and few cases of childhood diabetes, it might be difficult to assemble a complete multidisciplinary team. ISPAD recommend that in cases like these, care should be provided by a locally based pediatrician or physician who can lean on regional centers with more facilities and resources (24).

5.1.8. Treatment of diabetes

Children with T1DM require administration of exogenous insulin because of the destruction of their pancreatic islet cells and lack of endogenous insulin production. During the first few weeks after diagnosis the endogenous insulin secretion may recover for a short period of time. This is often referred to as the “honeymoon period” and calls for tightly controlled BG and often a reduction or even full stop in the insulin administration (25). Nutrition is an important aspect of the diabetes management and consists of meal planning, carbohydrate counting and understanding how meals affect the BG.

5.1.8.1. Insulin treatment

Insulin was first used as treatment of T1DM in 1922 (26). The physiologic secretion of insulin in a non-diabetic individual is difficult to mimic accurately. A non-diabetic has a constant basal secretion of insulin with bursts of insulin secretion, e.g. after meals. With the introduction of several new insulin preparations since 1996, insulin therapy options for diabetics have expanded. Insulin therapies can now more closely mimic physiologic insulin secretion and thus achieve better glycemic control in patients with diabetes (27). Insulin is administered either subcutaneously or intravenously.

5.1.8.1.1. Insulin preparations

The types of insulin can be classified by their onset, peak and duration of action (25):

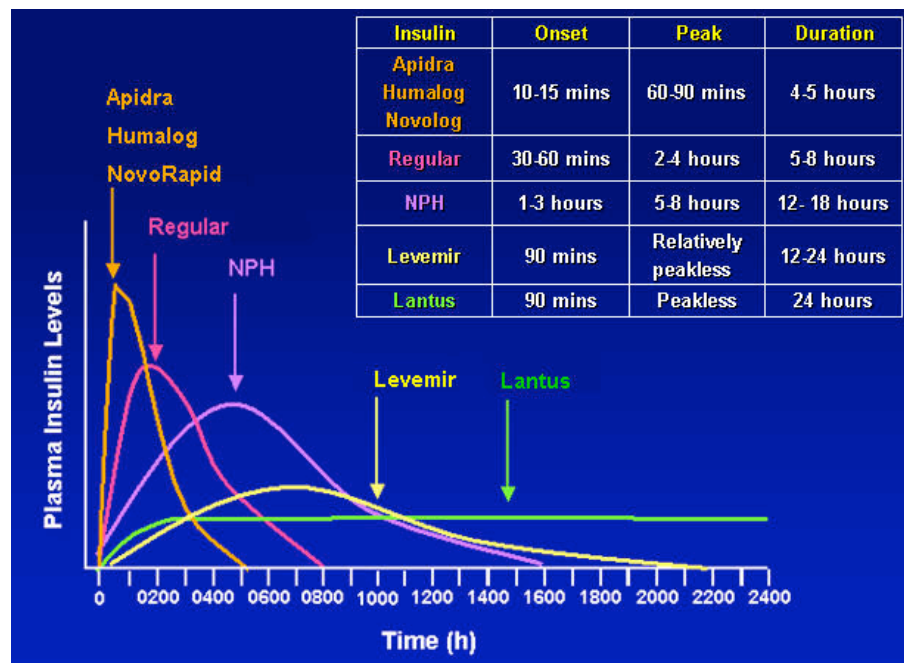


Fig.4. Comparison between different insulin types and their profile (29)

- **Rapid-acting and short-acting insulin types:**
 - Typically administered as a pre meal bolus based on the carbohydrate content of food and the BG level.
 - Provide basal insulin levels when delivered by continuous subcutaneous infusion via an insulin pump.
 - Commonly used preparations:
 - Rapid-acting analogues: Insulin lispro (Humalog®), Insulin aspart (Novolog®, Novorapid®).
 - Short-acting analogues: Human regular insulin (Humulin®S), soluble insulin.
- **Intermediate-acting insulin:**
 - Usually given two or three times a day.

- May be given in combination with long-acting insulins.
 - Provides some coverage for meals e.g., NPH (Neutral Protamine Hagedorn) insulin given before breakfast will cover lunch.
 - Commonly used preparations: Isophane (NPH®), Lente (Humulin®N)
- **Long-acting insulin:**
 - Given once or twice a day.
 - Provide a basal insulin level that suppresses hepatic glucose production and maintains near-normal glucose levels in the fasting state.
 - Commonly used preparations:
 - Long-acting: Ultralente (Humulin ®U)
 - Very long-acting: Detemir (Levemir®), Glargine (Lantus®)

5.1.8.1.2. Insulin administration

Insulin can be administered by syringe, pen or pump (25):

- **Needle and syringe**
 - An advantage of needle and syringe is that NPH and short- or rapid-acting insulins can be mixed in a single injection, thereby reducing the number of injections.
- **Pen**
 - Pens are supplied pre-filled with insulin and may be either disposable or reusable.
 - The ease of use and portability of pens are appealing to many patients.
- **Insulin pump (continuous subcutaneous insulin infusion (CSII))**
 - Insulin pump therapy is at present the best way to imitate the physiological insulin profile (10).
 - Rapid- or short-acting insulin is infused through a subcutaneously inserted catheter.
 - The insulin is delivered at set intervals to provide a pre-programmed basal-rate.
 - Boluses of insulin are added to counterbalance postprandial rise in BG and to correct out-of-range BG levels.
 - Information on insulin administration, frequency of catheter site changes, and frequency and timing of pre-meal insulin boluses can be downloaded from a memory chip within the pump. This is very helpful for guidance of glycemic control, both for the patient at home and at follow-ups.
 - Insulin pump therapy relies on frequent blood glucose monitoring and appropriate adjustment of insulin infusion rates.
 - Insulin pumps have not yet incorporated a "closed loop" system in which blood glucose values are determined and automatically used to reprogram the insulin pump.

5.1.8.1.3. Insulin regimens

There are multiple insulin regimens with variations in insulin preparations, administrations and number of insulin injections throughout the day.

- **Conventional regimens**
 - Usually “two injections daily” or “three injections daily” with administration of an intermediate-acting insulin (NPH) at least twice a day and with a rapid- or short-acting insulin two or three times a day (30).
 - The patient and family must adjust their lifestyle so that meals and exercise occur on a relatively fixed daily schedule, as the regimens are fixed.

- **Intensive regimens**
 - Insulin administrations that aim at mimicking the physiologic insulin secretion more closely by maintaining a basal insulin level and add additional pre-meal and pre-snack boluses of rapid- or short-acting insulin to minimize postprandial elevation of BG.
 - The boluses are adjusted according to the carbohydrate content of meals as well as the current BG level and expected level of exercise after the meal.
 - Allows more flexibility in terms of timing and carbohydrate content of meals compared to the conventional regimens, but demands increased involvement of the patients and families. Without proper education, increased BG monitoring, increased frequency of insulin administration, carbohydrate counting and judging of the impact of physical activity on insulin requirements, the benefits of following an intensive regimen might not be attained (25).
 - The choice of intensive regimen delivered either by multiple daily injections (MDI) or by CSII, is based upon patient, family, and clinician preferences (25).
 - Demonstrated by controlled studies (e.g. the Diabetes Control and Complications Trial (DCCT)) to achieve better glycemic control and reduce the incidence of long-term sequelae in adults and adolescents compared to conventional insulin therapy (10, 25, 31).
 - Reported by observational studies to be a safe, effective and superior alternative to conventional regimens with improved glycemic control in children (32, 33).
 - Is recommended that to be selected whenever possible (25).

5.1.8.1.4. Choice of insulin regimen – multiple daily injections (MDI) versus continuous subcutaneous insulin infusion (CSII)

A systematic review comparing CSII versus MDI for T1DM was published in The Cochrane Library in 2010. The review looked at 23 studies that had randomized 976

participants with T1DM to either intervention. The main results were (34):

- There was a statistically significant difference in glycated hemoglobin (HbA1c) favoring CSII.
- There were no obvious differences between the interventions for non-severe hypoglycemia, but severe hypoglycemia appeared to be reduced in those using CSII.
- Quality of life measures suggest that CSII is preferred over MDI.
- No significant difference was found for weight.
- There was insufficient evidence regarding adverse events, mortality, morbidity and costs.

Observational studies have reported improved glycemic control and fewer episodes of hypoglycemia with CSII compared with previous insulin regimens, both conventional and MDI therapy, in children and adults. Beneficial use of insulin pump therapy has been reported in children as young as two years of age. On the other side, several small controlled trials comparing CSII to MDI have shown no difference in glycemic control and frequency of hypoglycemic episodes in children. The following reports describe some of the beneficial effects of insulin pump therapy (25):

- A meta-analysis reported a reduction in severe hypoglycemia and improvement in HbA1c in patients with T1DM using CSII compared with MDI (35).
- A randomized controlled trial (RCT) of 32 children demonstrated that insulin pump therapy compared to MDI resulted in lower HbA1C levels (7.2 versus 8.1 percent) (36).

Many children and their families prefer the pump to injection therapy. CSII demands the same amount of increased effort as MDI, but the MDI regimen may require as much as six to seven injections per day, which may be a barrier for some children. The insulin pump also appears to improve quality of life (34).

In May 2011 BestPractice published a summary comparing CSII and MDI based upon five systematic reviews published during the time 2005-2009 (37). BestPractice concludes that CSII may be more effective than MDI at improving HbA1c, some quality of life measures and that it may reduce the frequency of severe hypoglycemia in those adult patients at highest risk. Because of low-quality evidence BestPractice do not conclude about the effects in adolescents. In the summary they have not reported on observational studies, but state that these studies have shown a much greater benefit with CSII than that observed in RCTs. Results of the observational studies were included by the National Institute for Health and Clinical excellence (NICE) in the development of recent insulin pump therapy guidance (37).

Recent studies imply that the increased risk of diabetic ketoacidosis (DKA) reported with earlier generations of pump devices do no longer seem to be apparent (37). This may reflect both improvements in technology and improved diabetes education. There is insufficient evidence regarding the effects of long-term CSII use on complications and mortality.

5.1.8.1.5. Whole pancreas and pancreatic islet transplantation

Transplantation of pancreatic tissue to individuals with T1DM allows them to be independent of the daily insulin injections. Although it is still an experimental procedure, it may represent a future therapy of T1DM. The main disadvantage is the need for major lifelong immunosuppressive therapy.

- Whole pancreas transplantation is usually performed when individuals with T1DM develop end-stage renal disease (ESRD) as simultaneous pancreas-kidney transplantations. The majority of pancreas transplantations (>90%) are pancreas-kidney transplantations (38).
- Pancreatic islet cell transplantation is performed by harvesting pancreatic islets from cadavers and injecting them into the portal vein. The islet cells reach and seed themselves into the liver. This remains an experimental therapy, but experience is accumulating (28).

5.1.8.2. Nutritional management and carbohydrate counting

An important aspect of the diabetes management is giving the children with T1DM and their families good advice on what to eat. The children should learn good nutritional habits that can be implemented in their everyday life and practiced lifelong. It is important to include the whole family to achieve good compliance. Current practice regarding nutritional advice in pediatric diabetes is recommending a general healthy diet, as research on this topic is limited. Diabetes education should include teaching on how carbohydrates, fat and proteins affect blood glucose as well as basic dietetic advice. ISPAD guidelines recommend having a dietician in the multidisciplinary team (39).

ISPAD recommendations of distribution of total daily energy	
Carbohydrate	50–55 % <ul style="list-style-type: none"> • Moderate sucrose intake (up to 10%)
Fat	30–35% <ul style="list-style-type: none"> • <10% saturated fat + trans fatty acids • <10% polyunsaturated fat • >10% monounsaturated fat (up to 20 %) • n-3 fatty acids (cis configuration): 0.15 g /day
Protein	10–15%

Table 5 International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendations of distribution of total daily energy (39)

Nutritional management can aid in glycemic control:

- Meal planning or keeping a food plan with qualitative and quantitative advice on food intake can be useful.
- Carbohydrate counting can be a good way of keeping control of the BG level and is used frequently as an alternative to a meal plan especially amongst patients on MDI or CSII.

- The patients on intensive insulin regimes use an insulin-to-carbohydrate ratio (“carb ratio”) to calculate the dosage of insulin for each meal or snack (57).
- Keeping a weight that is appropriate for the patient’s age and gender will be helpful in regulating metabolism as well as improving quality of life (40).

Basic advice on diet from the CDA CPG:

- Three meals per day at regular times and no more than six hours apart. A healthy snack might be beneficial.
- Limit sugars and sweets.
- Limit the amount of high-fat food.
- Eat more high-fiber foods.
- If thirsty, drink water.
- Add physical activity to your life

5.1.8.3. Physical activity

Physical activity is a natural part of the everyday life in most children, and with only a few exceptions (e.g. diving) children with T1DM should be able to do the same activities and sports as other children. The insulin demand decreases with increased level of physical activity and the insulin dosage must be adjusted to correspond with the amount of carbohydrates eaten and the level of exercise. Knowledge about how exercise influences the level of blood glucose is important to convey when educating children with T1DM and their families (41) as the level of physical activity may be reduced as a consequence of fear of hypoglycemia (42).

Children and adolescents with T1DM are at increased risk of developing cardiovascular disease in older age compared with their non-diabetic peers. The atherosclerotic process starts in childhood and is accelerated in patients with T1DM. Youth with T1DM present early signs of atherosclerosis, as well as low physical activity level and cardiorespiratory fitness (43). Physical exercise improves lipoprotein profile, increase insulin sensitivity, lower blood pressure and improve cardiovascular fitness and quality of life in persons with T1DM (44). A study done in Switzerland showed that endothelial function is enhanced in patients with T1DM who practice more than 60 min/day of moderate- to-vigorous physical activity. Motivating and supporting children and adolescents with T1DM to practice regular physical exercise is important (43).

5.1.9. Assessment and monitoring of glycemetic control

Monitoring of glycemetic control includes both the everyday measurements of the BG levels at home as well as the periodic measurement of HbA1c to assess the overall glycemia. The aims of monitoring is to properly adjust the insulin management to decrease fluctuations and avoid out of range BG levels with risk of acute and late complications of hypo- and hyperglycemia. Another advantage of monitoring HbA1c is that the data collected from each diabetes centre can be benchmarked with national and international standards. This might improve the local diabetes care (45).

5.1.9.1. Monitoring of glycemic control

Self-monitoring of blood glucose (SMBG)

Measurement of immediate glycemic control is best determined by SMBG. SMBG requires only a small amount of blood onto a strip that gives a read-out from a BG meter. The blood is often obtained using a finger stick. The frequency of SMBG is associated with improved HbA1c. BG monitoring is however expensive and in many countries the cost relative to the cost of living may make this technology unavailable. The ISPAD recommendations (45):

- SMBG should be made available for all children with T1DM when financially possible
- SMBG should be prescribed at a frequency to optimize each child's diabetes control, usually 4–6 times a day
- Centers caring for children with T1DM should urge nations, states, and health care providers to ensure that children and adolescents with T1DM have adequate glucose monitoring supplies.

Monitoring of urine glucose

Monitoring of urine glucose by using urine test strips is the only monitoring method available in many countries. Urinary glucose reflects glycemic levels over the preceding several hours, is affected by the renal threshold for glucose and has several limitations compared to SMBG (45).

Continuous subcutaneous glucose monitoring (CSGM)

While the SMBG determines the present capillary BG levels, the CSGM measure interstitial fluid glucose at set intervals. Minimally invasive devices are available, but currently expensive and may not be available in many countries. The devices have sensors subcutaneously that transmit readings to a receiver for readout. CSGM devices may particularly benefit those with hypoglycemic unawareness. As CSGM becomes more widely available, it is anticipated that decreased HbA1c targets may be achieved more safely, allowing further decreases in target HbA1c levels and improved outlooks for children with T1DM (45).

Monitoring urinary or blood ketones

ISPAD Guidelines state that urine or blood ketone testing should be performed during episodes of (45):

- Uncontrolled hyperglycemia
- Insulin deficiency
- Illness with fever and/or vomiting (sick days)
- BG values >14mmol/l in an unwell child
- Persistent polyuria with elevated BG or urine glucose, especially if symptoms of DKA are present.

Ketone levels can be determined by testing the urine for acetoacetate with strips or tablets or by testing the blood for levels of b-OH-butyrate with meters. There are meters available for testing of both ketone and capillary BG levels (two different strips). Blood ketone testing is especially important for pump patients as they have a

much smaller subcutaneous insulin depot, and therefore are at risk of developing ketosis if insulin delivery is interrupted for any reason (45).

5.1.9.2. Record keeping of glycemic control

Keeping record of glycemic control is useful for the patient's own adjustments of insulin treatment and for discussing at the time of consultation. The causes of variability in BG levels can be focused on in addition to making strategies for improving glycemic control. ISPAD Guidelines recommend that the record book should contain time and date of (45):

- BG levels
- Insulin dosage
- Special events affecting glycemic control
- Hypoglycemic episodes
- Episodes of ketonuria/ketonemia

5.1.10. Defining glycemic targets

5.1.10.1. Glycated hemoglobin (HbA1c)

HbA1c reflects the level of glycemia over the preceding 4–12 weeks (45). Glucose becomes irreversibly attached to the molecule of hemoglobin during the life cycle of the circulating red cell (which is approximately 120 days) forming glycated hemoglobin. HbA1c monitoring has been shown to be the most useful measure in evaluating metabolic control and is the only measure for which good data are available in terms of its relationship with later microvascular and macrovascular complications (45).

5.1.10.2. HbA1c targets

According to the ISPAD guidelines the target HbA1c for all age groups is recommended to be less than 7,5%. This recommendation is based upon the results from the DCCT study that intensive treatment lowers the risk of long-term complications. This target is intended as a guideline and each child should individualize its targets. Adolescents in their late teens should approach targets similar to adults (less than 7%) (45).

While ISPAD recommend equal target HbA1c for all age groups, the CDA and the ADA both recommend age-adjusted glycemic targets due to the increased risk of hypoglycemia associated with lower HbA1c (20, 46, 47 + table 6).

CDA recommendations of glycemic targets for children and adolescents with T1DM		
Age (years)	HbA1c (%)	Considerations
<6	<8,5	Extra caution is required to minimize hypoglycemia because of the potential association between severe hypoglycemia and later cognitive impairment
6-12	<8,0	Targets should be adjusted to the child's age
13-18	≤7.0	Appropriate for most adolescents

Table 6 Canadian Diabetes Association (CDA) recommendations of glycemic targets for children and adolescents with type 1 diabetes mellitus (T1DM) (20)

ISPAD recommendations concerning HbA1c measurements (45):

- Regular quality control comparisons with national and DCCT standards.
- Facilities for measurement of HbA1c should be available to all centers caring for children with T1DM.
- Every child should have a minimum of one measurement per year. (Ideally; 4-6 measurements/year in younger children and 3-4 measurements/year in older children).

5.1.11. Acute and late complications of T1DM

T1DM is a lifelong condition that can lead to both short-term (acute) and long-term complications. T1DM is also associated with a number of comorbid conditions. The most common short-term or acute complications include hypoglycemia, hyperglycemia, DKA, and psychiatric disorders (46). The age of onset and severity of long-term complications varies hugely and clinical manifestations of these are rarely seen in childhood. The focus in this thesis will be upon the complications that occur in childhood.

5.1.11.1. Hypoglycemia

Hypoglycemia is one of the most common acute complications of T1DM, and is most often a result of a mismatch between insulin dose, food intake and exercise (48). Hypoglycemia can result in immediate signs and symptoms, permanent sequelae or rarely, even death. The occurrence of hypoglycemic episodes can lead to fear of recurrence and be a major limiting factor in attempts of reaching near normal BG and HbA1c levels (48, 49).

Definition

According to the ISPAD guidelines there is no consistent or agreed definition of hypoglycemia for the child with diabetes. BG levels below 3,3-3,9mmol/L place the individual at risk for severe hypoglycemia. ADA and ISPAD agree upon recommending the lower target for BG in children and adults with T1DM as 3,9mmol/L (48). The CDA CPG define hypoglycemia by:

- 1) The development of autonomic or neuroglycopenic symptoms;
- 2) A low BG level (<4.0 mmol/L) and
- 3) Symptoms responding to the administration of carbohydrate

Signs and symptoms

The brain depends upon glucose for energy. Hypoglycemia results in the release of counter regulatory hormones such as glucagon, epinephrine, cortisol, and growth hormone (46). The signs and symptoms of hypoglycemia are often divided into neurogenic (sympathetic neural activation and epinephrine release) and neuroglycopenic (direct effect of hypoglycemia on the central nervous system). Children may also exhibit behavioral or mood changes when their BG falls, but remains over the normal level (48).

The BG threshold for activation of autonomic signs and symptoms is related to the activation of the counter regulatory hormones of hypoglycemia. This threshold can be affected by antecedent hypo- or hyperglycemia, exercise or sleep, and thus lead to a decrease in symptoms of hypoglycemia during a period of time (48). This condition, called *hypoglycemia unawareness*, is defined as neuroglycopenia occurring before autonomic activation, as the BG threshold for neuroglycopenia neither varies as much with the level of glucose control nor with antecedent hypoglycemia. Hypoglycemia unawareness can lead to reduced awareness of the onset of hypoglycemia and thus result in more severe episodes. Prevention of hypoglycemia for a few weeks can restore hypoglycemia awareness (46, 48).

Signs and symptoms of hypoglycemia	
Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion and poor judgment
Sweating	Weakness
Pallor	Drowsiness
Anxiety	Vision changes
Hunger	Difficulty speaking
Nausea	Headache
Tingling	Dizziness and unsteady gait

Table 7 Signs and symptoms of hypoglycemia (46, 48)

Severity of hypoglycemia

Hypoglycemia has often been described as mild, moderate, or severe based on the individual's ability to treat oneself. However, mild and moderate hypoglycemia is often considered together as there are no clinically reasons to distinguish between them and because younger children will almost always need to be treated by a parent or caregiver (48).

Treatment

The goal of treatment is to restore euglycemia. Because of the risk of rebound hyperglycemia and overweight, it is important to avoid overtreatment. Treatment of hypoglycemia should be provided promptly. Immediate intake of oral, rapidly absorbed, simple carbohydrate is often sufficient. Severe hypoglycemia may require parenteral therapy (glucagon or i.v. glucose). The amount of carbohydrate required will depend upon the size of the child, type of insulin therapy and proximity to recent insulin dosage and exercise (4).

Brain dysfunction, neurologic sequelae and mortality

Some studies have shown that hypoglycemia can lead to permanent central nervous system (CNS) changes and a decrease in cognitive function in children with T1DM, particularly in those diagnosed before the age of 5-6 years (45, 46). Recently, there

has been an increased interest in the role of early-onset T1DM and chronic hyperglycemia (48). Some studies question the impact of hypoglycemia on long-term declines in cognitive function (46). A long-term follow up of the DCCT cohort found no evidence of substantial long-term declines in cognitive function, despite relatively high rates of recurrent severe hypoglycemia. In this study a large group of patients with T1DM was carefully followed for an average of 18 years (50).

Sudden nocturnal death in young persons with T1DM has been described and is known as the ‘dead in bed’ syndrome. Nocturnal hypoglycemia has been implicated as a possible cause for these deaths (48).

Risk of hypoglycemia-targets for prevention

To avoid episodes of hypoglycemia, it is important that the child and family receives education about the risk factors and times when hypoglycemia is more likely to occur, so that they can be alert and initiate more frequent BG monitoring (20, 46, 48).

Risk factors associated with hypoglycemia in patients with T1DM
<ul style="list-style-type: none"> • Age of the patient (infancy and adolescence) • Degree of glycemic control (lower HbA1c) • Insulin regimen (higher insulin dose) • Alteration of the treatment regimen (more insulin, less food and more exercise) • Exercise • Timing, frequency, and carbohydrate content of meals • Acute illness • Psychological and socioeconomic factors including patient education and self-care behavior • Occurrence of a prior hypoglycemic episode • Increased duration of diabetes • Hypoglycemia unawareness • Autonomic neuropathy • Sleep • Alcohol consumption • Comorbidities (celiac and Addison’s disease)

Table 8. Risk factors associated with hypoglycemia in patients with type 1 diabetes mellitus (T1DM) (20, 46, 48).

A summary published by BestPractice in May 2011 and a systematic review published by The Cochrane Library in 2010 comparing CSII versus MDI for T1DM both reported that CSII may reduce the frequency of severe hypoglycemia compared to MDI (34, 37).

5.1.11.2. Hyperglycemia and diabetic ketoacidosis (DKA)

Hyperglycemia is a fairly common complication of T1DM and can be potentially fatal if DKA develops. Hyperglycemia occurs with postprandial relative insulin deficiency or at times with increased insulin needs, like during physiologic stress. If hyperglycemia is not adequately treated with additional insulin therapy, the body will begin lipid breakdown with the production and accumulation of ketoacids (2).

Clinical manifestations of DKA

- Dehydration
- Rapid, deep, sighing (Kussmaul respiration)
- Nausea, vomiting, and abdominal pain mimicking an acute abdomen
- Progressive obtundation and loss of consciousness
- Increased leukocyte count with left shift
- Non-specific elevation of serum amylase
- Fever only when infection is present

Table 9. Clinical manifestations of diabetic ketoacidosis (DKA) (2).

DKA results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counterregulatory hormones: catecholamines, glucagon, cortisol and growth hormone (28). DKA can be present at the initial presentation of T1DM. Patients who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason. However, recent studies imply that the increased risk of DKA reported with earlier generations of pump devices no longer seem apparent (37). Monitoring BG and ketone levels regularly and especially during times of stress can prevent DKA.

ISPAD	CDA
Biochemical criteria for the diagnosis of DKA	No definitive criteria for the diagnosis of DKA
-Hyperglycemia (blood glucose >11 mmol/L -Venous pH <7.3 or bicarbonate <15 mmol/L -Ketonemia and ketonuria	Typically: -Arterial pH ≤7.3 -Serum bicarbonate ≤15mmol/L -Anion gap >12 mmol/L - Ketonemia and ketonuria - BG usually ≥14.0 mmol/L, but can be lower

Table 10. Criteria for the diagnosis of diabetic ketoacidosis (DKA) (20).

5.1.11.3. Late complications

The late complications of T1DM lead to increased morbidity and mortality in addition to reduced quality of life and major health costs. Most of the available experimental and clinical evidence suggests that the late complications of T1DM are a consequence of metabolic derangements, mainly hyperglycemia (53).

The late complications of T1DM and their outcomes	
Complication	Outcome
Vascular disease	Cardiac disease Peripheral vascular disease Stroke
Nephropathy	Renal failure Hypertension
Neuropathy	Pain Paresthesiae Muscle weakness Autonomic dysfunction
Ocular complications	Retinopathy Cataracts Glaucoma Visual impairment Blindness

Table 11. The late complications of type 1 diabetes mellitus (T1DM) and their outcomes (53, 54).

5.1.11.4. Growth

Most children with T1DM grow normally. Poor glycemic control is associated with reduced weight and height, delayed skeletal and/or pubertal development (Mauriac syndrome) and hepatomegaly (non-alcoholic steatohepatitis). Conversely, excessive insulin can lead to weight gain and obesity. Monitoring of growth and physical development and the use of growth charts is essential in diabetes care.

5.1.11.5. Psychiatric disorders

The negative psychological impact of the diagnosis of T1DM on children and adolescents has been well established (46). Depression and eating disorders are not uncommon. Children with T1DM have a two-fold greater prevalence of depression and adolescents up to three-fold greater, than their non-diabetic peers (51). In data from the Danish Diabetes Registry, T1DM was a risk factor for attempted suicide (52). Adolescent girls with T1DM are more likely to develop an eating disorder compared to girls without T1DM. Patients may skip insulin injections to induce weight loss (46).

5.1.12. Comorbid conditions and autoimmune diseases associated with T1DM

Children and adolescents with T1DM are at increased risk for developing comorbid conditions and autoimmune diseases, most commonly thyroid and celiac disease (46). Primary hypothyroidism due to autoimmune thyroiditis occurs in approximately 3–8% of children and adolescents with diabetes. Celiac disease occurs in 1–10% of children and adolescents with T1DM (55).

Comorbid conditions and autoimmune diseases associated with T1DM
<ul style="list-style-type: none">• Thyroid disease• Celiac disease• Dyslipidemia• Necrobiosis lipoidica diabetorum• Limited joint mobility• Menstrual irregularities• Paronychia• Calcium, vitamin D and bone changes• Vitiligo• Primary adrenal insufficiency (Addison's disease)• Lipodystrophy (Lipoatrophy and lipohypertrophy)• Oedema (rare)

Table 12. Comorbid conditions associated with type 1 diabetes mellitus (T1DM) (46,55).

According to ISPAD guidelines, routine clinical examination should be undertaken for skin and joint changes.

5.1.13. Screening for complications and comorbidity

Screening for diabetes complications aims to detect subclinical complications that may be treated to delay progression to clinical disease (54). The pathogenesis of diabetic vascular complications begins at diabetes onset, but the conditions that the changes may lead to remain subclinical for years. Screening for late complications is important because children and adolescents with T1DM rarely present with symptoms in the early stages of diabetes. Early detection of subclinical changes allows for intervention, such as improved glycemic control or secondary prophylaxis of the different organ systems with targeted treatment (46).

Screening for and prevention of complications			
Complication	Indications and intervals for screening		Screening method
	CDA	ISPAD	
Nephropathy	T1DM >5 years: Yearly screening from age 12 years	-T1DM >2 years: start at age 11 years -T1DM >5 yrs: start at age 9 years -Yearly screening	Microalbuminuria: -Albumin/creatinine ratio (ACR). First morning urine (preferred) or random ACR -Albumin concentration (AC) - Albumin excretion rate (AER) in timed, overnight or 24-hour split urine collections
Retinopathy	-T1DM >5 years : Yearly screening from age 15 years -Screening interval can increase to 2 years if good HbA1c, duration of T1DM <10 years, and no retinopathy at initial assessment	-T1DM >2 yrs: from age 11 years -T1DM >5 yrs: from age 9 years -Generally yearly screening, more frequently if high risk features. - Biannually if good HbA1c, duration of T1DM <10 years, and no retinopathy at initial assessment	- Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil (minimum assessment) -Digital fundus photography -7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard)
Neuropathy	- Postpubertal adolescents with poor HbA1c should be screened yearly after 5 years' duration of T1DM		Question and examine for symptoms of numbness, pain, cramps and paresthesia, as well as skin sensation, vibration sense, light touch and ankle reflexes.
Dyslipidemia	-Delay screening until HbA1c has stabilized -Screen at age 12 and 17 years -Age <12 years of age: screen only those with BMI >95th percentile, family history of hyperlipidemia or premature CVD	-Delay screening until HbA1c has stabilized -Screen at age 12 and then every five years -screen at age 2 years if family history of hypercholesterolaemia, early CVD or unknown family history	Fasting total cholesterol, HDL cholesterol, triglycerides, calculated LDL cholesterol
Hypertension	-At least twice a year	- At least annually	-Use appropriate cuff size

Table 13. International Society for Pediatric and Adolescent Diabetes (ISPAD) and Canadian Diabetes Association (CDA) recommendations for screening for and prevention of complications (20, 54).

ISPAD recommends initial eye examination shortly after diagnosis to detect cataracts or major refractive errors which require treatment. ISPAD do not discuss screening for neuropathy, but recommend clinical assessment of neuropathy involving history taking and physical examination (54).

Because patients with T1DM are at risk of developing other autoimmune diseases, both ISPAD and CDA recommend screening for thyroid, celiac and Addison disease (20, 55).

Recommendations for screening for comorbid conditions in children with T1DM				
Condition	Indications for screening	Screening test	Frequency	
			CDA	ISPAD
Auto-immune thyroid disease	All children with T1DM	Serum TSH level + thyro-peroxidase antibodies	At diagnosis and every 2 years thereafter	At diagnosis and every 2 years thereafter in asymptomatic individuals.
	Positive thyroid antibodies, thyroid symptoms or goiter		Every 6–12 months	More frequent than biannually
Addison disease	Unexplained recurrent hypoglycemia and decreasing insulin requirements	8 AM serum cortisol + serum sodium and potassium	As clinically indicated	
Celiac disease	All children with T1DM	Tissue Trans-glutaminase + Immune-globulin A levels	As clinically indicated	At diagnosis -Annually for the first 5 years of T1DM, then every second years
	Recurrent gastrointestinal symptoms, poor linear growth or weight gain, fatigue, anemia, unexplained frequent hypoglycemia, poor HbA1c or first-degree relative with celiac disease.			More frequent assessment

Table 14. International Society for Pediatric and Adolescent Diabetes (ISPAD) and Canadian Diabetes Association (CDA) recommendations for screening for comorbid conditions in children with type 1 diabetes mellitus (T1DM) (20, 55).

6. PART TWO

– A comparative study between Norway and Canada

6.1.Introduction and background

The numbers and facts presented in this part two of our thesis are mainly based upon our clinical observations and interviews with the employees who we met at the hospitals in Norway and Canada. The Norwegian Childhood Diabetes Registry (NCDR) cooperates with all of the 26 pediatric wards in Norway that work with children and adolescents with diabetes. The NCDR publish an annual report based on reports and results from the different wards that describe the Norwegian national care of diabetes in children and adolescents. Because of the lack of a national diabetes register in Canada, most of the facts and numbers from Canada are based upon information from the employees at the hospitals and are thus less precise than the Norwegian data.

6.1.1. Hospital presentation

6.1.1.1. Oslo University Hospital, Ullevål (OUS)



OUS is the largest hospital in Norway, with more than 20 000 employees. After a merge in September 2009 OUS now consists of what used to be four different hospitals in the city of Oslo; Rikshospitalet, Radiumhospitalet, Aker University Hospital and Ullevål University Hospital. OUS is affiliated with the Medical Faculty at the University of Oslo. About 50 % of the medical research that is done at Norwegian hospitals originates here (56).

OUS has more than 1,2 million patient contacts every year and gives medical service to the population in Oslo and the greater regional area of the south-eastern part of the country. The hospital also provides national services. The pediatric department at OUS, Ullevål has 415 employees and offers a wide variety of medical services. The pediatric medical ward has 22 beds for inpatient treatment and a pediatric endocrinology outpatient clinic where the children with DM are followed up. They care for more than 300 children and adolescents with DM every year. In 2009 there were in total 310 patients out of which 294 had T1DM, 6 T2DM, 8 MODY and 2 Kir 2.6 (15).

6.1.1.2. BC Children's Hospital (BCCH), Vancouver, British Columbia, Canada



BCCH is situated just outside the city center of Vancouver in the westernmost province of Canada, the British Columbia. The hospital received more than 196,000 patient visits in 2009. In 2009, the total daily visits per month to BCCH increased by over 30,000 or more than 12 % since 2006, perhaps reflecting the growth in

population. The hospital receives patients from a vast geographical area, and 67 % of patients seen every year at BCCH come from areas outside the city of Vancouver. (56). The BCCH is affiliated with the University of British Columbia (UBC) Faculty of Medicine (57).

The BCCH care for more than 1000 children and adolescents with DM every year. In 2009 there were in total 1023 patients out of which 926 had T1DM, 46 T2DM, 7 MODY and 42 other DM subtypes (62).

6.1.1.3. Hospital for Sick Children (SickKids), Toronto, Ontario, Canada



SickKids is located in the city centre of Toronto. The hospital provides the population of Toronto and the Ontario Province with medical care and is affiliated with the University of Toronto.

Every year, approximately 15,000 children stay at SickKids in close to 400 beds; almost 300,000 visits are made to more than 100 clinics; emergency staff treats 50,000 children and 13,000 operations are performed (58). About 1000 children with T1DM are followed at SickKids out of which about 940 has T1DM. These children come from the Greater Toronto Area for the most part. The staff at the Diabetes Clinic at SickKids travels once a year to far northern Ontario (59)

6.1.2. The Norwegian Childhood Diabetes Registry (NCDR)

Norway has a national registry for pediatric and adolescent (0-18 years) diabetes, NCDR, established in 2006 with a conjunction of the Norwegian Diabetes Registry and the “Pediatric Diabetes and Quality”. The NCDR is based on the “Norwegian Studygroup for Childhood Diabetes”, a network of pediatricians and nurses specializing in and working with DM.

The NCDR is based on a signed consent from the child and the parents. All types of DM are included in the registry and data is collected from every reported new case (incidence rates). When a child is newly diagnosed with DM a standardized form of notification is filled out and sent to NCDR. The form contains information on age, sex, ethnical background, familial heredity, other diseases, height, weight and pubertal stadium, lab-works, treatment given at the ward and what treatment the child will have at discharge.

Every year all 26 pediatric wards in Norway that treats children and adolescents with diabetes send rapports with the results from an annual examination of their patients to the NCDR. From 2008 all pediatric departments in Norway have participated. The rapports are standardized forms with documentation of questionnaires and clinical examination. A rapport is returned to each ward with their local data and a national rapport with benchmarking results. The numbers of patients participating in the yearly examinations has been rising since the beginning of registration in 2001. The percentage of participating patients in the annual examination in 2009 was 92%

(range 54-100%). The registry has data from 1973 on incidence rates and is a database for research (14).

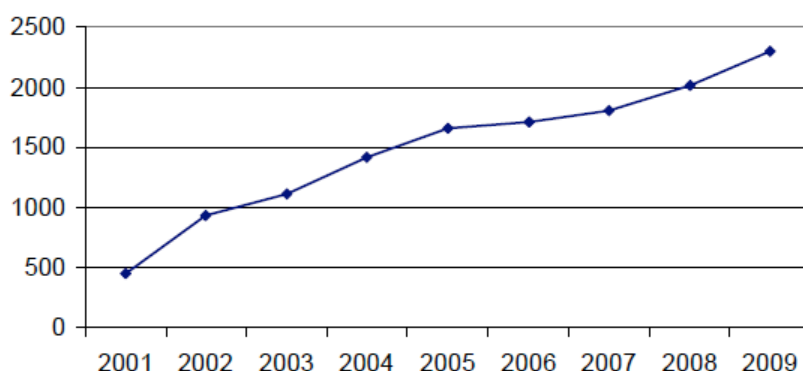


Fig. 5. Number of patients participating in the annual diabetes controls in Norway 2001-2009 (14)

6.2. Results

6.2.1. Diabetes education and follow-up at diagnosis

OUS

When a child is diagnosed with T1DM at OUS, he or she is admitted for an average inbed length of stay of 11 days, together with his/hers parents. Depending on the child's condition, age and family the period may vary from 6 to 14 days. Initial treatment is started and the child and the family receive education from the diabetes team during this first stay at the hospital. They have separate appointments with each of the professional members of the diabetes team (doctor, diabetes nurse, dietitian, social worker, psychologist). The doctor treating the child in this initial stay will continue as this patient's doctor in the years to come. The diabetes team consider this initial stay at the hospital very valuable as the child, its family and the diabetes team get to know each other very well. During this initial stay the patient sleeps at home for some of the nights. This is a part of the education allowing the family to learn how to deal with their new situation while the diabetes team can control that the family establishes good routines. The doctor will often give his or her personal phone number to the family to make the family feel confident and secure. The staff at OUS finds that there are several advantages of hospital admittance after diagnosis, especially that the patient and family feel safe and taken good care of. The members of the diabetes team are able to build a trustworthy and close relationship with the child and the parents and can follow them closely to make sure that they comprehend the education and manage the diabetes care properly. The diabetes nurses do visits to schools and kindergardens (15).

BCCH

BCCH provides families with a newly diagnosed child with T1DM a Diabetes Day Program (DDP) which is a full three days program where the child's primary caregivers together with the child receive education on how to manage T1DM. The family is not hospitalized but stays in a close by hotel. The child is served all meals at the hospital and the parents are instructed in insulin injection techniques, type and

dosage of insulin etc. A diabetes nurse educator together with a dietitian is responsible for this training. They do all insulin injection, check the BG levels and do the urine checks. Between the meals the family is educated on different topics concerning the management of T1DM. Physicians, a social worker and psychologist are also part of the diabetes team (57).

SickKids

Children who are newly diagnosed with T1DM come as outpatients with their families to the diabetes day care unit at the hospital for two days from breakfast till supper. The child is assigned a core team consisting of one nurse, a physician and a social worker. The first two days the family receives initial education that consists mostly of one-to-one teaching, but sometimes also group teaching. After the first two initial days, the family has four following sessions spaced with one week. Each session is three hours; one hour with the doctor and two hours with the nurse. Sometimes they see the social worker or psychologist, according to the individual child's or family's needs. Their first clinic visit is approximately 6-8 weeks after the diagnosis. After this they receive follow-ups every three months (59).

After the day care and when the family has proven that they manage the insulin therapy, they are discharged from the hospital and receive a contact telephone number to their designated nurse. The family is advised to test the blood glucose four times a day and report the 24h BG. The family will usually call their nurse every day for the first two weeks and then less frequently for insulin dosage advice and for general advice (e.g. concerning special activities like sports or birthday parties). The family will usually provide the school/kindergarten with the information they need, but the staff from the core team can do school visits if there are any difficulties (59).

6.2.2. Diabetes multidisciplinary team

There are many similarities on the composition of diabetes teams in Norway and Canada (table 15). The Norwegian Diabetes Association has made a national standard for diabetes teams in Norway describing the team's tasks and composition (60) and the Norwegian Ministry of Health and Care Services made a national strategy for diabetes in the years 2006-2010 emphasizing the importance of the diabetes team in the management of DM (61). The most common health workers of the team in both Canada and Norway are: physicians with a specialty in pediatrics and special knowledge on diabetes, nurses with special knowledge on diabetes, dietitians, a social worker and a psychologist. This is in accordance with the ISPAD and CDA guidelines. Table 15 shows a comparison of the composition of the diabetes multidisciplinary teams between the hospitals in Norway and Canada.

6.2.3. Follow-up

OUS

Patients at OUS are seen by their physician and most often a diabetes nurse at the pediatric outpatient clinic every three month or more frequently if needed. The diabetes team is available by telephone 24 h for advice. Social workers, dietitians or psychologists are not seen on a regular basis, but called on when needed. The patient keeps a diabetes diary that he or she brings to the consultation. This makes a basis for discussion and targeted follow up. Special problems or concerns are discussed. The

focus is both on what is good and what is not so good. At every consultation the HbA1c is measured and the physician looks for lipohypertrophy (fatty lumps) in the skin. Once a year growth charts and developmental stages are recorded (15).

BCCH

In BCCH, they would ideally see the children less than 5 years of age every three months and the older children every six months. In reality they saw the youngest children every four months and the older ones every eight months. Patients living far away would usually attend BCCH once a year and ideally see their local pediatrician in between visits to measure their HbA1c every three months. The patients all have 24 h access to a member of the diabetes team in case of emergencies. The nurses are available over phone, fax or e-mail and receive about 200 phone calls every week. Once a year the diabetes team would travel to one or two cities in distant areas of the province, e.g. Edmonton or Calgary. The no-show rate at BCCH was 5-10% (62).

SickKids

At Sick-Kids they usually see their patients every three months. The children mostly come from the Greater Toronto Area, with a mean travel time of 30-60 minutes. A few families living outside of Toronto chose to do their follow-ups at SickKids.. About once a year the diabetes team travels to distant areas of the province, e.g. far northern Ontario (59).

	OUS	BCCH	SickKids
Who makes the diagnosis?	General practitioner or hospital doctor	Usually the General practitioner	Hospital doctor
Admission at diagnosis?	Admission 11 days on average	Only if presenting with diabetes ketoacidosis	Only if presenting with diabetes ketoacidosis
Composition of the diabetes multi-disciplinary team	-Physicians with special interest in pediatric diabetes (every child have a primary assigned physician) -3 diabetes nurses (210 % position) -2 social workers (2x20 % position) -1 dietitian (40 % position) -1 psychologist (50 % position)	-5-6 nurses -6 physicians -2 dietitians -1 social worker -psychologist available	-7 physicians (usually pediatric endocrinologist) -5 diabetes nurses -3 diabetes dietitians -1 social worker or counselor -Psychologist (part time)
Education	-At the time of diagnosis. - Most often individual, separate appointments with each of the members of the diabetes team. -Group sessions with parents twice a year for all newly diagnosed last six months. -Once a year group sessions with every 12 year old patients without their parents.	-At the time of diagnosis. (Diabetes Day Program - outpatient). -Re-education is given individually and in groups. Once a month group teaching for patients living far away, they can stay overnight.	-At the time of diagnosis. Diabetes Day Care (outpatient). -Access Clinic for teenagers with HbA1c% >10 for more than two visits in a row, open two days a week, diabetes team available.
Follow-up	-After diagnosis and discharge from the hospital they come in for an appointment after one week, next one after two weeks, then after four weeks, two months and then every 3 month. -Daily telephone contact first period after diagnosis.	<5 years: every 3 month (but in reality every 4 month) >5 years: every 6 month (but in reality every 8 month)	-Every 3 month

Table 15. A comparison between Oslo University Hospital (OUS), BC Children's Hospital (BCCH), Vancouver and Hospital for Sick Children (SickKids), Toronto in regards to admission at diagnosis, composition of the diabetes multidisciplinary team, education and follow-up.

6.2.4. Treatment – choice of insulin regimens

OUS

Data from the NCDR annual report in 2009 show that almost all the children with T1DM in Norway are on an intensive insulin regimen (table 16). Approximately two thirds of the youngest children (under 5 years) are on pumps.

	Age (years)				Total
	<5	5-9	10-14	>15	
Diet only	0	0	0	0	0
Antidiabetes tablets	0	0	0,1	0,5	0,2
Insulin pen	35,3	47,5	44,3	51,8	47,2
Premixed	0	0,5	0,6	0,7	0,8
Insulin pump	64,7	52,0	55,1	47,5	52,0

Table 16. Number of patients (%) with type 1 diabetes mellitus that are on the different types of diabetes treatments (14).

The percentage of children that use insulin pumps in Norway varies between the pediatric wards, with a range from 13-81%. (fig. 7). Every child that is diagnosed with T1DM at OUS is offered an insulin pump regardless of the child's age. In 2009, 62% of the children with T1DM at OUS were on pumps. Close to all of the remaining 38% children are on MDI. Almost no child use less than three daily injections. Most of the patients on MDI use pens as opposed to syringes (14).

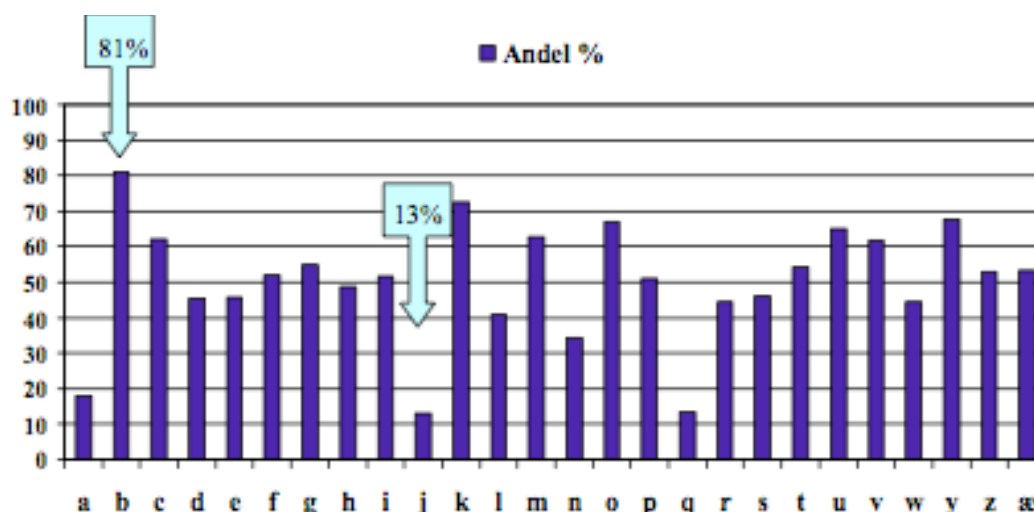


Fig.6. The portion of patients (%) on insulin pump therapy in the different pediatric wards (a-æ) in Norway at the annual examination in 2009 (14)

The data from Canada is based on numbers from a database on BCCH and from interviews with the staff at SickKids (table 16).

Insulin regimen	OUS	BCCH	SickKids
Insulin pump	62%	32 %	30(-40)%
MDI	38%	4 %	10%
Conventional regimens (injections)	0	64 %	50-60%

Table 16 Choice of insulin regimen at the Oslo University Hospital (OUS), BC Children's Hospital (BCCH), Vancouver and Hospital for Sick Children (SickKids), Toronto.

BCCH

At BCCH all the patients are started on a conventional regimen with a combination therapy of NPH and short-acting insulin. They are encouraged to use pens, but get the choice of using syringes. The staff at BCCH prefers to have known the family for a year and that the child has had T1DM for a year before they offer changing to CSII, unless the family ask for and wants a pump (62).

SickKids

All the children at SickKids are started on insulin injection therapy, regardless of the age of the child, except perhaps if the child has a sibling who uses an insulin pump. The government finances the pumps and some of the pump supplies when the child has had T1DM for a year and when certain criteria are met (e.g. three clinic visits in a year, HbA1c less than 10%). The family and child are assessed at the time of diagnosis to consider if MDI are an appropriate treatment. If not, the insulin treatment is simplified and the patients are put on a two-injections-daily regimen (59).

6.2.5. Glycemic control and glycemic targets

OUS

The study group in NCDR follows the ISPAD recommendation of HbA1c < 7,5% in children 0-18 years. In 2009 the annual report from NCDR shows that the mean HbA1c was 8,7% in Norway and 8,6% in OUS. The mean HbA1c in the different departments are benchmarked (14).

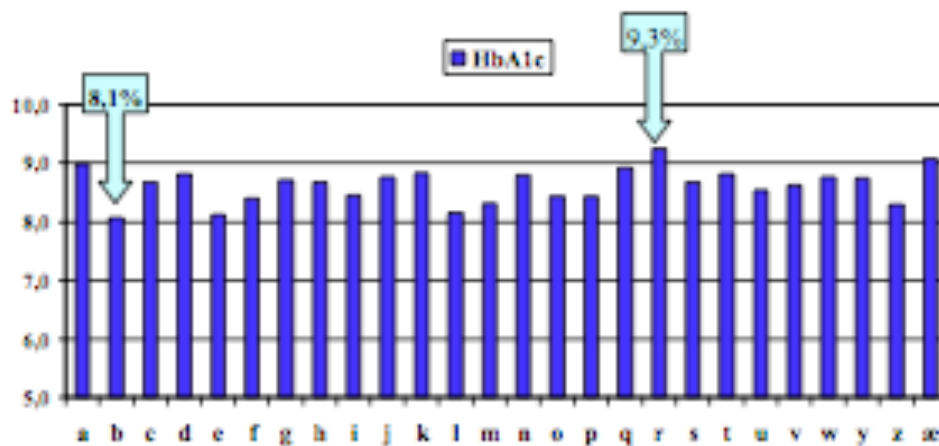


Fig.7. HbA1c from the different Norwegian pediatric wards caring for children with diabetes (a-æ) measured at Aker University Hospital in 2009 (14).

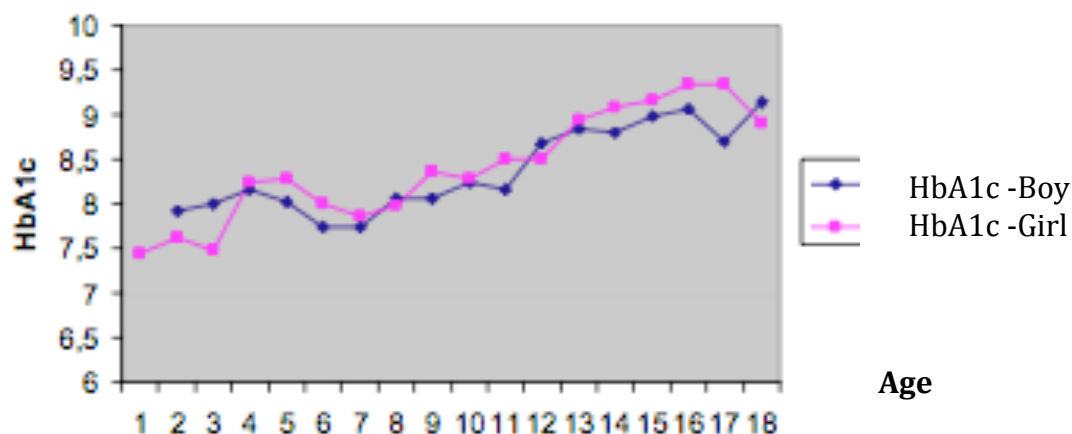


Fig.8. HbA1c measured at Oslo University Hospital, OUS, Aker in 2009, distributed on age and sex of the patients (14)

BCCH and SickKids

Both BCCH and SickKids follow the CDA CPG in regards to glycemic targets. CDA recommend age-adjusted glycemic targets due to the increased risk of hypoglycemia with lower HbA1c. The mean HbA1c was reported by the staff at BCCH and Sick Kids to be 8,3% in 2009. It is not known if these hospitals do benchmarking on HbA1c.

6.2.6. Complications

The most serious acute complications that can arise in children with T1DM are severe hypoglycemia with unconsciousness and/or seizures and diabetes ketoacidosis (DKA) from hyperglycemia. Both complications are due to failure of proper insulin dosage to the BG level, with either too little insulin (leading to hyperglycemia) or too much insulin (leading to hypoglycemia). The NCDR register number of patients hospitalized with DKA, severe hypoglycemia and hypoglycemia that requires help from another person (14).

Number of patients presenting with DKA at diagnosis %			Number of patients hospitalized with DKA % (numbers)			Number of patients hospitalized with hypoglycemia % (numbers)			Number of patients with hypoglycemia that requires help % (numbers)
NCDR	Sick Kids	BCC H	NCD R	Sick Kids	BC CH	NCDR	Sick Kids	BCCH	NCDR
25	18	20	5 (113)	5-12	-	7 (155)	10-15	-	8 (166)

Table 17. The occurrence of diabetes ketoacidosis (DKA) and hypoglycemia in 2009 in Norway (The Norwegian Childhood Diabetes Registry (NCDR)) and in Canada (British Columbia Children’s Hospital (BCCH) and Hospital for Sick Children (SickKids)) (14, 59, 62).

The number of patients on insulin pumps has increased from 15% to 52% in Norway over the years 2002-2009. There has not been an increase in DKA during this time (14).

6.2.7. Screening for autoimmune diseases and late complications

Because of the correlation of the duration and level of hyperglycemia and degree of complications, optimal diabetic control is important from the time of diagnosis and throughout life. Childhood and adolescence is a period during which intensive education and treatment may prevent or delay the onset and progression of complications (54). The DCCT showed a 60% reduction in developing complications over 9 years when the HbA1c was kept at around 7 % in T1DM (31).

Norway adheres to the ISPAD recommendations for screening of late complications and comorbidity. At SickKids they do not screen for comorbidity until puberty or when the patients have had the diagnosis for more than 5 years and are more than 12 years of age. They then screen every two years or more frequent if the patients have positive findings (18). At BCCH they screen more often. According to Dr. Metzger they take both the CDA and ISPAD Guidelines into consideration as the ISPAD Guidelines are published more recently (2009 compared to CDA from 2008). Both thyroid and celiac disease are screened for biannually or if clinically suspected. Screening for retinopathy and nephropathy starts at age 10 or after five years of T1DM (62).

	NCDR (Yearly screening) Number of patients (%) screened in 2009	SickKids	BCCH
Nephropathy	86%	T1DM >5 years: Yearly screening from age 12	Yearly at age 10 or after 5 years of T1DM
Retinopathy	35%	When clinically indicated	Yearly at age 10 or after 5 years of T1DM
Thyroid disease	98%	Yearly for hypothyroidism	At diagnosis and then biannually
Celiac disease	98%	Once in year of diagnosis, then biannually or if suspected	At diagnosis and then biannually

Table 18 Screening for late complications and co morbid conditions in type 1 diabetes in children 0-18 years in Norway (The Norwegian Childhood Diabetes Registry (NCDR) and Canada (British Columbia Children’s Hospital (BCCH) and Hospital for Sick Children (SickKids)) (14, 18, 62).

6.3. Discussion

6.3.1. Hypoglycemia-parental fear

Fear of hypoglycemia can result in poor glycemic control. While attending diabetes clinics in Canada, we met multiple families that struggled with the dilemma of whether to keep the BG levels higher than the recommended targets in order to prevent hypoglycemic episodes or try to keep the BG levels at recommended lower levels and thus increasing the risk of experiencing hypoglycemic events. Quite a few of the families of the youngest patients attending clinics admitted to giving their child a snack when SMBG would show BG levels at 4,5 or even higher. Some of these children were slightly overweight. Based upon our observations attending diabetes

clinics, we wondered whether there could be an association between parental fear of hypoglycemia and children with poor glycemic control.

Dr. Denis Daneman at SickKids defines three issues to suggest why hypoglycemia can be an obstacle to keeping glycemic control (10):

1. *Fear of hypoglycemia.*
 - Often interferes with an individual's ability to achieve near-normal glycemic concentrations
 - Might be based on previous experiences with hypoglycemia or it may be part of wider anxiety about diabetes.
2. *Hypoglycemia unawareness*
3. *Episodes of severe hypoglycemia*
 - Predisposes to further episodes, as a result of downgraded regulatory responses to repeated hypoglycemic events.
 - Reassessment of glycemic targets and perhaps the insulin regimen is needed.

A systematic review looking at fear of hypoglycemia in parents of young children with T1DM was published in 2010 (63). The aim was to systematically review studies concerning the extent and consequences of fear of hypoglycemia in parents of children less than 12 years of age with T1DM and interventions to reduce such fear. Knowing that patients and families are afraid of hypoglycemia, they hypothesized and aimed to evaluate the effectiveness of any interventions designed to prevent that (49):

1. Fear of hypoglycemia might take precedence over concern about long-term complications.
2. Behavior to avoid hypoglycemia might be at the cost of poorer control.

Results and conclusion from this review:

- Parental fear of hypoglycemia, anxiety and depression are common, affecting both parental health and quality of life.
- Hypoglycemia avoidance behaviors by parents might adversely affect glycemic control.
- No interventions that reduced parental fear of hypoglycemia were found.
- Trials of interventions to reduce parental anxiety and hypoglycemia avoidance behavior are needed.

It is important to uncover and address parental fear of hypoglycemia at an early stage, so that the parents feel secure and safe in managing the diabetes care of their child. The diabetes team at OUS finds that the diabetes education and the relationship being built between the diabetes team and family at the hospital during the first week after diagnosis is extremely valuable in order to make the family and child feel confidence and to reveal and address areas of uncertainty in regards to diabetes management (15).

6.3.2. Diabetes education and follow up

Follow-up at diagnosis

While OUS admit all children with newly diagnosed T1DM regardless of the presence of DKA, BCCH and SickKids do not admit children with newly diagnosed

T1DM unless they present with DKA at the time of diagnosis. In Canada both the hospitals we visited offer an outpatient educational program that the children attend together with their parents. The programs are similar with regards to what they teach the patients in Norway and Canada. At OUS the patient is admitted to the hospital with an average length of stay of 11 days. While this could initially seem as economically expensive, the knowledge about the particular child and family and the safety that the family feels is considered to be very valuable in the future diabetes management and follow-ups.

Diabetes education

At all of the three hospitals we visited the patients and their parents were given an initial education at the time of diagnosis. In BCCH many of the patients receive most of the education from local pediatricians, but they are offered to come in for teaching sessions with an overnight stay at BCCH. At OUS and SickKids most of the education is given at the hospital. All three hospitals give families a telephone number for close contact the first period after diagnosis. OUS was the only hospital where doctors gave away their personal phone number to the patients. We did not get the impression that patients or parents abused this way of contact.

Diabetes multidisciplinary team

There are many similarities on the composition of diabetes teams in Norway and Canada. The most common health workers of the teams are physicians with a specialty in pediatrics and special knowledge on diabetes, nurses with special knowledge on diabetes, dietitians, a social worker and a psychologist. This is in accordance with the ISPAD and CDA guidelines.

Follow-up

While attending clinics in Canada we found that one of the differences between the hospitals was who the children saw at check-ups and how much time spent with each member of the team. While many of the patients at BCCH would travel around ten hours to come to check-ups, the families at SickKids would rarely travel more than four hours. Mean travel time for the patients at OUS is very short, seldom more than two hours. Because the children and families followed at BCCH often would have had to travel far to get to the clinics, they would try and spend at least an hour and a half with the patients. At SickKids we found that they would be more time efficient. One of the doctors at SickKids said that at a normal day at the diabetes clinic he would see 30-50 patients, aiming at keeping the number under 40.

At OUS a regular check-up includes about 30 min with the physician and five to ten min with the diabetes nurse.

At OUS and SickKids the children are seen every three month. In BCCH we were told that they see their patients more seldom, the youngest children under five years they try to see every three month but in reality they see them every four month. The children over five years they try to see every sixth month, but in reality they see them every eight month. According to ISPAD guidelines a child with T1DM should be seen at least three to four times a year. BCCH does not meet this recommendation with every patient. We got the impression that this is at least partly because of the long travel distances in British Columbia.

6.3.3. Choice of insulin regimens

In controlled studies (e.g. the DCCT) intensive regimen has been demonstrated to achieve better glycemic control and reduce the incidence of long-term sequelae compared to conventional insulin therapy. It is recommended to be selected whenever possible (20, 24, 30, 31).

More emphasis has been on intensive insulin regimens ever since the DCCT showed reduced complication rates with tighter glycemic control. A systematic review published in The Cochrane Library in 2010 comparing CSII versus MDI for T1DM found that there was a statistically significant difference in HbA1c favoring CSII over MDI (34).

At OUS almost two thirds of the children with T1DM were on pumps, compared to both the Canadian hospitals were only one third of the children were on pumps. More surprisingly, about two thirds of the children are on conventional regimens, compared to almost none at OUS. This is, however, according to CDA guidelines (20). While ISPAD guidelines recommend consideration of an intensive insulin regimen (30), CDA guidelines recommend that children with new-onset diabetes should be started on at least 2 daily injections of short- or rapid- acting insulin analogues combined with an intermediate- or long-acting insulin. CDA recommend that the insulin therapy should be assessed at each clinical encounter to ensure that it still enables the child to meet HbA1c targets, minimizes the risk of hypoglycemia and allows flexibility in carbohydrate intake, daily schedule and activities. This assessment should include consideration of a change to CSII therapy. According to CDA CSII is safe and effective and can be initiated at any age (20). While every child that is diagnosed with T1DM at OUS is offered to start with an insulin pump at diagnosis, both the Canadian hospitals we visited preferred to wait for a year before putting the child on such therapy. The staff claimed that they preferred to have known the child and family for a year to consider if they are qualified for managing CSII therapy. In Ontario the government finances the pumps only when the child has had T1DM for a year (59). This might influence the choice of postponing pump therapy.

At BCCH we learned that there are no school nurses in Canada, but that they have a nursing support services system (the “NSS”) that look after children, generally from preschool until end of 3rd grade. These are not nurses, but they keep an eye on the children with T1DM; make sure that they eat their snack and measure the BG levels, but they don’t give insulin in school. According to Dr. Metzger at BCCH there is nowhere in Canada where the school personal can press the button on the insulin pumps or give injections of insulin in schools. Either the children have to do it with guidance from a caretaker over the phone, or someone has to come to school to do it for them. This is, according to Dr. Metzger, one of the reasons why they don’t have many kids on MDI (62). According to Janet, one of the diabetes nurses at SickKids, this also applies for their patients. Because no one in school can press the button on the insulin pump for the children at lunchtime or supervise the children while they push the button themselves, only a few of the youngest children are on pumps. This is a rare problem in Norway where the children often will have the staff in the school or kindergarten assisting them with their insulin administration. We found it unfortunate that such circumstances could influence whether or not children with T1DM is recommended and receives the best therapy available. While every child at OUS is

offered to start with a pump at diagnosis, the family and ideally the child have to want the pump and ask for it to get it at SickKids (59).

6.3.4. Glycemic control and glycemic targets

Glycemic control

The DCCT and similar studies provides clear evidence that better glycemic control in adults and adolescents, as measured by a lower HbA1c level, is associated with fewer and delayed microvascular complications. The DCCT showed a 60% reduction in developing microvascular complications over nine years when the HbA1c was kept at around 7 % in T1DM (31). ISPAD state that there is no reason to believe that this is not also the case in younger children (30).

Glycemic targets

While ISPAD recommend equal target HbA1c for all age groups, the CDA and the ADA both recommend age-adjusted glycemic targets due to the increased risk of hypoglycemia associated with lower HbA1c (20, 46, 47).

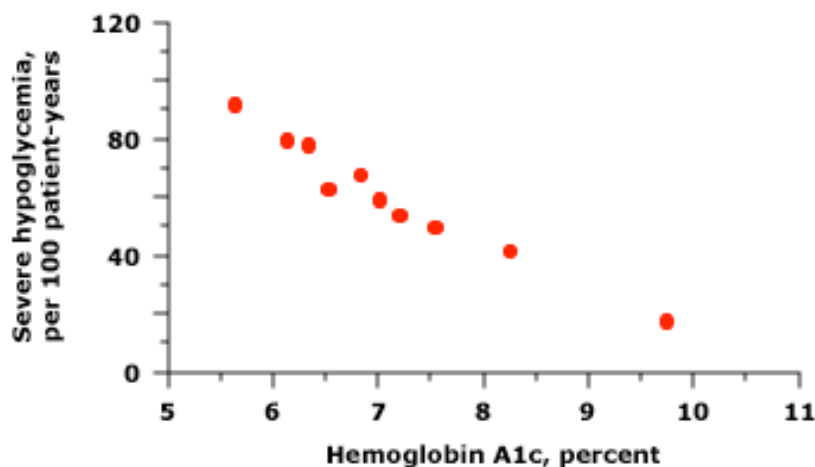


Figure 9. In the diabetes control and complications trial group (DCCT), there was a progressive increase in the incidence of severe hypoglycemic episodes (per 100 patient-years) at lower attained HbA1c values during intensive insulin therapy in patients with type 1 diabetes mellitus. Data from The DCCT Research Group (31)

Comparison of ISPAD, ADA, and CDA recommendations of HbA1c goals in children and adolescents with T1DM		
Age (years)	HbA1c (%)	
	ADA and CDA	ISPAD
<6	<8,5	<7,5%
6-12	<8,0	
13-18	≤7.0	

Table 19 Recommendations of HbA1c in children and adolescents with type 1 diabetes mellitus (T1DM) according to International Society of Pediatric and Adolescent Diabetes (ISPAD), American Diabetes Association (ADA) and Canadian Diabetes Association (CDA). (20, 47)

According to ISPAD there is evidence in many studies that the risk of hypoglycemia increases as the HbA1c decreases, but this is not always the case. The ISPAD guidelines state that glycemic control and the risk of hypoglycemia may be decreased by the choice of insulin regimens and the frequency of BG monitoring (e.g. severe hypoglycemia appeared to be reduced in those using CSII compared to MDI regimen (34)). Careful attention to avoid severe hypoglycemia is important, and it is recommended by ISPAD that when hypoglycemia unawareness is present, glycemic targets should be increased until hypoglycemia awareness is restored. The youngest children (under 6 years) are at increased risk for adverse neurologic outcomes from severe hypoglycemia as they are unable to self-identify hypoglycemia, ISPAD state that caution in achieving lower targets for younger children is appropriate (45).

Short-term risks of hypoglycemia include potentially dangerous circumstances that may arise when someone is hypoglycemic, e.g. while climbing a tree. Long-term consequences of severe, long lasting or repetitive hypoglycemia might include mild cognitive impairments in teenagers with early onset T1DM or older adults with longstanding disease. (45). Controversy remains about whether cognitive effects in young children are a result of severe hypoglycemia or rather due to effect of chronic hyperglycemia (10).

In 2009 the mean HbA1c at OUS, SickKids and BCCH did not differ much (8,6% at OUS compared to 8,3% at both the Canadian Hospitals). However, the target for glycemic control varies between the different countries. While Norway adhere to the ISPAD guidelines of a target HbA1c < 7,5%, the Canadian Hospitals follow the CDA age-adjusted targets with higher target HbA1c for children less than 12 years of age. The goal of diabetes management should be to achieve a HbA1c value as close to normal as possible to avoid the long-term micro- and macrovascular complications of DM, while at the same time avoiding complications associated with both hypo- and hyperglycemia

6.4. Summary

During the last century T1DM in the western part of the world has evolved from being a fatal disease with certain death short time after diagnosis to becoming a disease that is rapidly increasing in incidence and associated with increased long-term morbidity and mortality. The US Centers for Disease Control recently estimated that a 10-year-old boy or girl developing diabetes in the year 2000 would lose, on average, 18,7 and 19,0 life-years, respectively, compared with non-diabetic peers (10). Optimal diabetes management is important to avoid or delay the long-term complications of DM. In addition to optimal diabetes treatment, tight glycemic control and avoidance of the short-term complications of diabetes while screening for long-term complications and co morbidities associated with diabetes, diabetes education remains a cornerstone in this work. The hospitals we visited in Norway and Canada all had well-organized diabetes care and did for the most part practice according to international guidelines of pediatric diabetes.

Diabetes treatment has evolved gradually after the discovery of insulin in 1922, but a cure for diabetes remains to be found. Intensive insulin regimens have been shown to achieve better glycemic control and reduce the incidence of long-term sequelae in

adults and adolescents compared to conventional insulin therapy (10, 24, 30, 31). It has also been demonstrated that CSII is favorable to MDI in terms of reaching lower HbA1c targets and possibly increased quality of life measures and reduced frequency of severe hypoglycemic events (34, 37). While every child diagnosed with T1DM at OUS is offered to start with an insulin pump at diagnosis, all the children at SickKids are started on insulin injection therapy and both the Canadian hospitals we visited preferred to wait for a year before beginning with CSII. Compared to OUS, where almost two thirds of the children with T1DM are on pumps, both the Canadian hospitals have only got one third of the children on pumps. More surprisingly, in Canada about two thirds of the children are on conventional regimens, compared to almost none at OUS. According to Dr. Metzger at BCCH one of the reasons why they don't have many children on MDI is because there is no one at school that can do the injections for them (18, 62).

The DCCT and similar studies, provides clear evidence that better glycemic control in adults and adolescents, as measured by a lower HbA1c level, is associated with fewer and delayed microvascular complications (31). While ISPAD recommend equal target HbA1c < 7,5% for all age groups, CDA recommend age-adjusted glycemic targets due to the increased risk of hypoglycemia with lower HbA1c. According to ISPAD there is evidence in many studies that the risk of hypoglycemia increases as the HbA1c decreases, but that this is not always the case.

Controversy remains about whether cognitive effects in young children are a result of severe hypoglycemia or rather due to the effect of chronic hyperglycemia (10). A systematic review looking at fear of hypoglycemia in parents of young children with T1DM showed that there is some suggestion that hypoglycemia avoidance behaviors by parents might adversely affect glycemic control (63). A thorough diabetes education, frequent follow-ups and a well-established relationship between the physician and the children with T1DM and their families can be helpful in uncovering and addressing parental fear of hypoglycemia at an early stage to ensure confidence and safe diabetes care.

6.5. Conclusion

Optimal diabetes management to avoid the short- and long-term complications is important as T1DM is a chronic condition associated with increased morbidity and mortality. Children with T1DM should, where possible, receive the best diabetes care available. Tight glycemic control and intensive insulin regimen has been shown to reduce and delay the diabetes late complications and should be included as part of the management of childhood diabetes.

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8. Appendix

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QUESTIONNAIRE – DIABETES (T1DM and T2DM) IN CHILDREN: A GLOBAL PERSPECTIVE

This questionnaire is designed to gather information about children less than 15 years of age with diabetes. The interview consists of two parts. Each part should not last more than 1 hour.

The first part is designed to map diabetes in children at a national or regional level, and the interviewer fills out this first part of the interview based on information available on the internet and other available sources. The information will then be quality assessed with the local informant.

The second part is designed to map how children with diabetes are followed up at the local hospital/treatment centre. The interview contains multiple open, qualitative questions. The interview will therefore be tape-recorded and the tape recordings will be transcribed before the analysis takes place.

The questionnaire does not ask for personal sensitive information.

QUESTIONNAIRE – DIABETES IN CHILDREN.....	
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Country:
Region/county/state:
Date:
Informant: name/occupation
Interview by:

PART 1

Incidence

1. The annual incidence of the different types of diabetes in this country (enter the number and percentage)
 - Type 1 diabetes (T1D)
 - Type 2 diabetes (T2D)
 - Gestational diabetes

2. The incidence of T1D and T2D among children under 15 years of age
 - The total incidence:
 - How is the distribution in the following groups of ages (estimated):
 - <5 years
 - 5-<10 years
 - 10-<15 years
 - > 15 years

3. What is the gender distribution among children with T1D and T2D in the country?

4. What are the overall proportions of the following ethnicities in this country:
 - White / European background (non-Hispanic whites)
 - Black / African background
 - Middle-East / North-African
 - Indian subcontinent
 - East-Asia
 - Middle- and South American (Hispanics)
 - Indigenous (specify)
 - Mixed (or unclassified)

5. How many children with diabetes in this country are
 - White / European background (non-Hispanic whites)
 - Black / African background
 - Middle-East / North-African
 - Indian subcontinent
 - East-Asia
 - Middle- and South American (Hispanics)
 - Indigenous (specify)
 - Mixed (or unclassified)

Prevalence

6. What is the prevalence of T1D and T2D among children in the following groups of age?
- <5 years
 - 5-<10 years
 - 10-<15 years
 - ≥ 15 (adults)

Mortality

7. What is the average life expectancy in the country?
- Women:
 - Men:
8. What is the average life expectancy among patients diagnosed with T1D before the age of 15?
- Women:
 - Men:

National health

9. How many doctors per citizen? (This will differ depending on location; city, rural, town etc)
10. Is there a geographical difference in availability of doctors?
11. What is the gross domestic product (GDP) of the county?
12. What is the total expenditure on health as a percentage of the GDP?
- Which proportion is financed by the public?
 - Which proportion is financed by private actors?
13. Which proportion of the national budget is spent on health?
14. Does the public health care system finance the costs associated with diabetes medication and equipment?
- Yes
 - No
15. If the answer is yes on question 14, which *medication* is financed?
- Insulin
 - Yes
 - _____% financed
 - No
 - Antidiabetic drugs

- Yes
 - _____% financed
- No

Glucagon

- Yes
 - _____% financed
- No

16. If yes on question 14, which of the following *materials* is financed

- Syringes:
- Needles:
- Insulin pen:
- Insulin pump:
- Materials for the unconsciousness insulin pump: (needle, catheter, reservoir etc):
- Home Blood Glucose meters:
- Blood glucose test strips:
- Finger-pricking devices:
- Lancets for finger-pricking:
- Continuous subcutaneous glucose monitoring devices:
- Urine sticks to check for ketonuria:
- Other: _____

17. If the answer is yes on question 14, does the patient have to pay anything? If so, how much? (%)

- Syringes:
- Needles:
- Insulin pen:
- Insulin pump:
- Materials for the insulin pump: (needle, catheter, reservoir...):
- Home Blood Glucose meters:
- Blood glucose test strips:
- Finger-pricking devices:
- Lancets for finger-pricking:
- Continuous subcutaneous glucose monitoring devices:
- Urine sticks to check for ketonuria:
- Other: _____

18. How brings the child to their check-ups?

- Mum
- Dad
- Other: _____ (specify)

19. Are there any laws/public rights for parents to get extra time off work to take their children to check ups?

- Yes
- No

20. Are parents with chronic ill children allowed to take additional days off compared to the general population?

- Yes (_____ number of additional days)
- No

21. Are there national guidelines for the management of children with T1D and T2D?

- Yes
- No

Patient organizations

22. Are there any national organizations for patients with diabetes?

- Yes
 - For children?
 - For children and adults?
 - For adults only?
- No

23. Are there any local organizations for patients with T1D?

- Yes
 - For children?
 - For children and adults?
 - For adults only?
- No

Comment:

24. What do the patient organizations offer the children and their parents?

- Websites
- Telephone
- Courses
- Information meetings
- Holiday offers
- Other: _____

Register for diabetes

25. Is there a national diabetes register?

- Yes, for children
- Yes, for adults
- Yes, for adults and children
- No

26. If yes, what data is registered?

Complications

27. What is the incidence of acute diabetes complications among children under 15 years of age?
- Diabetic ketoacidosis (with hospitalization)
 - Grave hypoglycemia (unconscious with or without convulsions)
28. What is the incidence of late diabetes complications among children under 15 years of age? (estimated percentage)
- Retinopathy
 - Nefropathy
 - Nevropathy

Country:
Region/county/state:
Local treatmentcenter (name and type):
Date:
Informant: name/occupation
Interview by:

PART 2

Hospitalizations and number of hospital beds

29. How many children <15 years with diabetes are admitted to hospital annually in the following wards (The total number of hospitalizations including rehospitalization)
- Pediatric ward
 - Adolescens ward
 - Internal medical ward
30. To what age are the children managed in the pediatric wards? _____
31. If there is an adolescent department, when do the children start attending and how long can they attend there?
32. What is the maximum number of beds in the ward? _____
33. How often has the ward been full during the last 6 months? (regardless of the reason for the hospitalisation)
34. How many children with diabetes are followed up at the local hospital today?
35. How is the gender distribution among the children that are followed up at the local hospital?
36. Who takes over the responsibility for the treatment and follow-up after the diagnosis of diabetes?
- Specialist _____ (which type)
 - General practitioner (GP)
 - Other : _____

Diagnostics

37. Who usually make the diagnosis?
- General practice
 - Specialised health service
 - Nurse
 - Other: _____
38. What is the average age at diagnosis?
39. What are the classical symptoms that make the patient and his or her parents contact a doctor?
40. Which diagnostic criteria have to be fulfilled to make the diagnose of diabetes?
- International guidelines; ISPAD (Blood glucose)
 - Other guidelines: _____
41. Where are recently diagnosed juvenile diabetics treated the first time?
- Out-patients clinic
 - Hospital ward with beds
42. If the patient is admitted to hospital, what is the average length of stay?
43. Which diagnostic criteria do you use for DKA?
- Hyperglycemia
 - Standard Bicarbonate (< 15 mmol)
 - pH (< 7,3)
 - Urine ketons
44. What proportion of children has DKA at diagnosis?

Treatment and follow up

45. Who participates in the treatment and follow up of children with diabetes?
- Nurse
 - Doctor
 - School nurse
 - Social worker
 - Nutritionist
 - Psychologist
 - Other: _____
 - Multidisciplinary team
46. Does the child with diabetes have one particular contact person? If yes, specify:
- Yes: _____
 - No

47. When the diagnosis is made who is responsible for the follow-up?
- Specialist (doctor / diabetologist)
 - Hospital doctor
 - Nurse
 - General practitioner
 - Other: _____
48. Who are educated (at the time of the diagnosis, and after discharge)?
- The child
 - Parents
 - School
 - School nurse
 - Nursery
 - Activity leaders/coaches
 - Others: _____
 - No one
49. Does the hospital have access to interpreters when they have patients that do not speak/understand English?
50. How is the education organized?
- Training in groups
 - Individual training
 - A combination of both
51. When is a new education organized? (re-education)
52. Is carbohydrate counting used systematically when calculating the insulin bolus in relation to food?
53. How is the education organized?
- Training in groups
 - Individual training
 - A combination of a and
- Comment:
54. How much do parents participate in the treatment and follow up?
55. Do the adolescents get contraceptive counseling?
- Yes (comment;) _____
 - No
56. Have you experienced unintended pregnancies in this group of patients?
- Yes (how many? what are the characteristics of these patients; ethnicity, socioeconomic status etc?)
 - No

57. What types of treatment/treatment regimens are available for children with diabetes at the local hospital?
- Syringes
 - Needles
 - Insulin pen
 - Insulin pump
 - Continuous Subcutaneous Glucose Monitoring
 - Others: _____
 - None
58. How many patients use multi injection (insulin > 3 times a day) therapy?
59. What proportion of the patients (in number and percentage) follow the different treatment regimens listed
- Insulin pump:
 - Others:
 - None:?
60. Among the children under multi injection therapy what type of insulin preparations are used? (%)
- Premixed insulin preparations
 - Intermediate-acting insulin + rapid-acting insulin
 - Analogues
 - Which combinations: _____
 - Are there any different strategies for insulin therapy concerning the child's age?
61. Who does the patient and his or her parents contact if the child is acute ill?
- Specialist
 - Contact person
 - GP
 - Emergency room
 - Other: _____

Treatment goals

62. Are the ISPAD treatment goals adhered to?
- Yes
 - No
 - If no, which guidelines are used _____
63. What are the treatment goals
- HbA_{1c} < 7,5 %
 - Other: _____

64. What proportions (%) of patients achieve the treatment goals?
65. How often do the children attend diabetes health check ups? _____
66. What proportions (%) of the patients attend their appointment?
- Most patients
 - 50 %
 - Only a few
67. Who does not attend? Why? What are the characteristics of these patients?
68. Is there a screening program for autoimmune diseases?
- Yes
 - No
69. If yes, witch diseases are included in the screening
- Celiac disease
 - Hypothyroidism / hyperthyroidism
 - Others: _____
70. If yes, how often is the screening performed
- At each check up
 - Annually
 - Other: _____
71. Are there any screening program concerning late diabetes complications among children with diabetes?
- Yes
 - No
72. If yes, what kind of late diabetes complications are included in the screening program among children with diabetes? And which methods are used in the screening
- Retinopathy: _____
 - Nephropathy: _____
 - Neuropathy: _____
 - Angiopathy: _____
 - Others: _____
73. If yes on question 70, how often is the screening performed
- At every check up:
 - Annually:
 - Other: _____

Quality of life and mental health:

74. What assistance do the children with diabetes and their parents receive in relation to:

- School
- Hobbies
- Sports

75. Are there social activities arranged for the children and their parents?

76. What kind of social activities are arranged? And who organises them?

77. Have you conducted/do you conduct research on the quality of life in the children with diabetes?

- Yes
 - If yes, can you elaborate
- No

78. Are intoxicants a problem among children with T1D?

- Yes
 - What kind of intoxicant?
 - What are the characteristics of these patients (gender, ethnicity, socioeconomic status etc)
- No

Comment:

Complications

79. What is the incidence (percentage) of acute diabetes complications among children with T1D under the age of 15?

- Diabetic ketoacidosis
- Hypoglycemic shock with unconsciousness and/or convulsions
- Other: _____

80. What is the incidence (%) of long-term complications among children under the age of 15 years? And how old are they?

- Retinopathy:
How many have been treated with laser?
- Nephropathy:
- Neuropathy:
- Hypertension
How many get anti hypertension treatment?

81. What is the incidence (%) of long-term complication among adults who got the diagnose of diabetes before they turned 15 years?

The following must be discussed:

- How old were the patients when they were diagnosed with diabetes?
- How many years diabetes duration at onset of the late complication?

- Retinopathy:
- Nephropathy:
- Neuropathy:

82. Is overweight a problem among children with diabetes?

- If yes:
 - Are there any differences between gender, ethnicity, socioeconomic background etc?
 - In which group is the prevalence of overweight highest?
 - What kind of prevention and treatment regimens does the hospital have?
 - Are the treatment regimens effective?
 - Do children with overweight in practice have significant more complications than children with normal weight?
 - Are there other problems related to overweight and diabetes?