Scope of epidemiology and daily practice in children with type 1 diabetes in the Netherlands

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CHAPTER 1

Introduction
**WHAT THIS THESIS IS ABOUT**

Job, a seven year old boy, was referred to the emergency department of our hospital. Since a few days his mother noticed that he had been drinking a lot and had been complaining of being very thirsty. He also had to pee frequently. Job wetted his bed occasionally, but in recent weeks his bed was already completely wet when his parents went to sleep. He had not eaten well last week, but he did eat a lot of yoghurt. According to his parents, Job seemed to have lost some weight. The family history did not show any relevant details. The whole family had had gastroenteritis two weeks earlier. On physical examination, we saw a very thin, skinny boy with sunken eyes. No further physical or behavioural abnormalities were noticed. The clinical suspicion of type 1 diabetes mellitus (based on the classical symptoms of polyuria and polydipsia) was supported by laboratory test results which showed a very high blood glucose level (48 mmol/L) without acidosis (blood that is acidified). The HbA1c value (a measure that reflects the blood glucose concentration of the preceding 2-3 months) was clearly elevated (83 mmol/mol). Glucose was also found in large quantities in the urine. A few weeks later, confirmation of the suspicion of autoimmune diabetes came from the results of autoantibody testing, which was positive for antibodies against the Langerhans islets in the pancreas which are responsible for the production of insulin in the human body.

The inevitable conclusion of all this information is that Job has newly onset type 1 diabetes mellitus. From now on his life and that of his family will change dramatically, with daily blood glucose measurements, insulin injections, concerns about the glucose values, fear and real threat of hypoglycaemic episodes and the risk of long-term complications including eye and kidney problems.

**Definition:**

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders characterised by high blood glucose levels over a prolonged period of time. Type 1 diabetes mellitus (T1DM) is the type of diabetes mellitus in which insufficient and eventually no insulin is produced. T1DM is one of the most common chronic diseases in childhood. The incidence differs considerably between countries, with the highest recorded incidence in Finland with 64.2 per 100,000 person-years in 2005 (1). T1DM has a major impact on quality of life and daily functioning for the affected children and their family. The management of this disease poses substantial demands on the children and family, leading to work restrictions, negative financial impact, anxiety and worries (2).

**History**

Between 1914 and 1916, the Romanian physiologist Nicolas Paulescu first extracted a pancreatic antidiabetic agent that he used to treat dogs, but his experiments remained unnoticed to the scientific world. His method to prepare pancreatic extract was similar to
the procedure described in 1919 by the American scientist Israel Kleiner (3). The discovery of insulin in 1921 by Banting and Best was a lifesaver, allowing for the first time a proper treatment for people with T1DM. These Canadian researchers were awarded the Nobel Prize for Medicine and Physiology in 1923 (4). In January 1922, a 14-year old boy named Leonard Thompson received the first injection of isletin, as the pancreas extract containing insulin was initially named. He suffered a severe allergic reaction, which on hindsight was not entirely unexpected due to the rather poor purification of the injected substance. The second injection 12 days later was successful (5). Until that time, T1DM was a fatal disease, which it still is in areas of the world where insulin is unavailable.

**Prevalence**

The estimated worldwide prevalence of T1DM in children younger than 15 years of age was almost 500,000 in 2013 (6). The average annual increase of incidence of T1DM worldwide was 2.8% per year during the period 1990-1999, with up to 79,000 new cases worldwide per year in children aged 0-15 years (7). In the USA, the incidence rate increased by 1.4% per annum (19.5 cases per 100,000 youth a year in 2002-2003 to 21.7 cases per 100,000 person-years in 2011-2012) (8,9).

As mentioned, the highest recorded incidence rate of T1DM in children was in Finland (64.2 per 100,000 person-years (2005)) (10). By contrast, the incidence in China and Venezuela is only around 0.1 cases of T1DM per 100,000 person-years (7,11). Recent studies showed a stabilization of the incidence rate in Finland in the period 2005-2011 (1); similar trends were found in Norway and Sweden (12).

Most well-designed and larger incidence studies are from the USA and Scandinavia. Unfortunately, reliable information is lacking concerning the prevalence and incidence in many developing countries. The International Diabetes Federation atlas estimates of worldwide prevalence of T1DM in children younger than 15 years of age are presented in Figure 1. Data from the Netherlands were available in three time periods, the most recent being from 1996 to 1999 (6). Table 1: The estimated prevalence in 1978–1980 and 1996-1999 was 70 per 100,000 person-years (13) and 80 per 100,000 person-years, respectively (14). Although all paediatricians caring for children with T1DM in the Netherlands have the clinical experience that the incidence of the disease has continued to increase since 1999, recent incidence and prevalence data on T1DM prevalence in children are unavailable.
**Introduction**

Figure 1: Type 1 diabetes mellitus in children and adolescents >> number of new cases of type 1 diabetes mellitus per 100,000 children and adolescents (0-14) per year (2017)
http://www.diabetesatlas.org/across-the-globe.html

Table 1: Incidence (95% CI) of T1DM in the Netherlands

<table>
<thead>
<tr>
<th>Countries/territories with</th>
<th>by Number of new cases of type 1 diabetes per 100,000 children and adolescents (0-14) per year</th>
<th>All countries/territories ranked by Number of new cases of type 1 diabetes per 100,000 children and adolescents (0-14) per year</th>
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<tr>
<td>0 – 4 years</td>
<td>6.8 (6.6 – 7.1)</td>
<td>6.4 (6.2 – 6.7)</td>
<td>12.9 (12.0 – 13.9)</td>
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<td>5 – 9 years</td>
<td>10.9 (10.3 – 11.6)</td>
<td>12.4 (12.0 – 12.7)</td>
<td>19.3 (18.0 – 20.7)</td>
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<td>10 – 14 years</td>
<td>14.3 (13.4 – 15.3)</td>
<td>18.1 (17.6 – 18.6)</td>
<td>24.2 (21.9 – 26.6)</td>
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<tr>
<td>Total (0 – 14 years)</td>
<td>11.1 (10.5 – 11.7)</td>
<td>12.4 (12.0 – 12.8)</td>
<td>No data</td>
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Pathogenesis of T1DM

In the pathogenesis of T1DM, a loss of pancreatic islet β cells leads to a progressive and eventually complete loss of insulin producing capacity in the individual (15). The autoimmune mechanisms leading to initiation of damage and complete destruction of β cells are only partly understood. The pathogenesis of this disease is complex and influenced by many factors (figure 2).

**Figure 2**: The natural history of type 1 diabetes – a 25-year-old concept revised
A re-creation of the model of type 1 diabetes, originally proposed in 1986, is shown in black. Additions and conjectures based on recent knowledge gains are shown in purple.


Most children presenting with T1DM have autoantibodies against pancreatic β cells or autoantibodies against insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma-associated autoantigen (IA2A) and zinc transporter 8 (ZnT8A) (16,17). These autoantibodies are often already present years before the clinical onset of T1DM (17).

Some genetic factors associated with an increased susceptibility to develop T1DM have been identified. Individuals with haplotypes HLA-DR3-DQ2 or HLA-DR4-DQ8 are more prone to develop β cell autoimmunity (18). What eventually triggers this autoimmunity is only partially known; genetic susceptibility is a definite factor, both in itself, but also by influencing the severity of response to environmental triggers (19).

At the moment, it is generally accepted that an environmental trigger is needed to activate the autoimmune destruction of pancreatic β cells (21). Several environmental factors have
been proposed in studies, including infections, especially viral infections with e.g. retrovirus and enterovirus (17). Studies examining the incidence of T1DM in relation to season of birth and season of disease onset may help to support associations with such environmental factors (20,21). An association with season of onset would point towards seasonal environmental factors triggering the immune response leading to T1DM. The Eurodiab study described seasonality with peak incidence in the winter in 21 of the 23 participating European countries (22). As the Netherlands has not been participating in this register since 1999, seasonality patterns in diagnosis of T1DM in the Netherlands are unknown.

Additional autoimmune diseases in T1DM
Patients having T1DM are more prone to develop other autoimmune diseases, the most common being autoimmune thyroid disease and coeliac disease. Less common are autoimmune gastric disease, Addison’s disease, autoimmune hepatitis, myasthenia gravis, pernicious anaemia, vitiligo, non-organ specific autoimmune disease and multiple autoimmune diseases (such as juvenile idiopathic arthritis, Sjögren syndrome, psoriasis and sarcoidosis) (24).

The prevalence of autoimmune thyroid disease (AITD) in a combined population of children and adults in Europe is estimated to be 3% for hypothyroidism and 0.75% for hyperthyroidism (23). In children with T1DM, detectable antithyroid antibodies were reported in 15%-19% of patients (25,26). Unfortunately, it is at present unknown what proportion of children with thyroid autoantibodies will develop AITD, with estimates ranging from 3% to 60% (24–26). The prevalence of overt thyroid disease in children in the Netherlands with and without T1DM is unknown.

Clinical presentation
Although T1DM can have its début in adulthood, the peak incidence age is in childhood and adolescence (27). Classical clinical features include polydipsia, polyuria, weight loss due to hyperglycaemia and sometimes polyphagia and blurred vision (28).

Other types of diabetes in children and adolescents include type 2 diabetes mellitus (T2DM), maturity onset diabetes of the young (MODY), Kir 6.2 diabetes, diabetes associated with cystic fibrosis and steroid induced diabetes.

T2DM is characterized by increasing insulin demand caused by increased insulin resistance resulting in a relative insulin shortage (instead of the absolute shortage in T1DM). However, this relative shortage occurs mostly in adults (29,30). Most T2DM cases become manifest when β cells are incapable of meeting this increased demand. A combination of hereditary, social, behavioural and environmental factors play a role in the aetiology of this disease (31). It is estimated that 8-45% of children with diabetes in the USA have T2DM, compared to approximately 2% in the Netherlands. This higher prevalence of T2DM in the USA is largely
explained by the much higher prevalence of overweight and obesity in the USA compared to the Netherlands, especially in minority populations (32).

MODY is a monogenic autosomal dominant defect in β cell function representing 1-2% of children with diabetes. MODY is characterized by hyperglycaemia starting at an age below 25 caused by impaired insulin secretion with minimal or no defects in insulin action (33).

Finally, any process that diffusely injures the pancreas can lead to diabetes, such as pancreatitis and trauma, endocrinopathies, drug or chemically induced glucose metabolism disorders, infection, genetic syndromes such as cystic fibrosis, and genetic defects in insulin action (32).

In this thesis, only children with T1DM will be studied.

Treatment options for glycaemic control
The mainstay of T1DM treatment is the exogenous replacement of insulin to compensate for the loss of endogenous insulin production. Achieving good glycaemic control (with blood glucose concentrations between 4.5 and 9 mmol/l) remains a major challenge in and for most patients, however. Ideally, insulin replacement therapy should mimic the physiological insulin secretion response as much as possible. In daily practice, however, finding and maintaining the balance between short-term complications (i.e. hypoglycaemic events, the risk of which increases with strict insulin management) and long-term adverse sequelae (microvascular complications such as retinopathy, renal failure and neuropathy, which are less likely with strict glucose management) is a struggle for patients and their families. A variety of treatment methods and schemes have been developed to improve and maintain optimal glycaemic control, mostly by subcutaneous insulin administration.

The two most commonly used treatment strategies are multiple daily injections (MDI) (Figure 3), combining a long acting insulin covering a basal need during the day with short acting insulin injections administered before the meals, and continuous subcutaneous insulin infusion (CSII) (26). CSII involves wearing a device (comprising an insulin pump and an infusion set, including a cannula for subcutaneous insertion and a tubing system to connect the insulin reservoir to the cannula) which provides a steady flow of short acting insulin into the body. The “basal flow” delivers insulin between the meals and at night, and bolus doses are administered to cover the food eaten and correct high blood glucose levels.

Figure 3: principle of multiple daily injections (MDI): the basal flow (grey horizontal bar) covers the insulin requirement overnight and between meals, the boluses (yellow humps) represent the extra insulin required to process glucose intake during breakfast (B), lunch (L) and dinner (D). Before sleep (BS)
Striving for optimal glycaemic control requires repeated or ongoing measurement of blood glucose levels, either by using a blood glucose meter (self-monitoring of blood glucose, SMBG) or with a real-time continuous glucose monitoring sensor subcutaneously (rtCGM).

Technological advances aimed at progressive integration of CSII and rtCGM are being made, especially in developed countries. Sensor-augmented pump systems are already being used in clinical practice, allowing automated stops of insulin delivery when glucose levels drop below a specified cut-off point (34). An even more sophisticated closed loop system with both lowering or stopping of insulin delivery in case of hypoglycaemia and increased insulin delivery in case of hyperglycaemia (thus increasingly mimicking the physiological function of the pancreas automatically) is expected within the next few years (35).

Besides these technical developments, there is the possibility of islet-cell transplantation or pancreatic transplantation, for example in patients with severe, life threatening hypoglycaemia, severe glycaemic variability and progressive diabetic complications. Improvements of transplant procedures and immunosuppressive regimens have led to better long-term results. In selected centres of pancreas-alone transplantation, five-year insulin independence rates of more than 50% have been described (36). Remaining challenges for larger scale implementation of this treatment include the shortage of human donor pancreases, the need for immunosuppression and the inadequacy of the islet isolation process (37). In the Netherlands, all children with T1DM are being treated with insulin using CSII or MDI so this thesis focused on this treatment.

**Treatment goals in children with T1DM**

According to the International Society of Paediatric and Adolescent Diabetes (ISPAD), the main goals of treatment of children with T1DM are to normalize growth and development and to reduce the risks of short- and long-term complications by optimal glycaemic control (table 2) (38). The long-term microvascular complications of T1DM are related to the degree of long-term metabolic dysregulation: the higher the HbA1c over a long period of time, the higher the microvascular complication risk. T1DM is also associated with an increased risk of macrovascular complications. This is only partly dependent on the degree of long-term metabolic control (38,39).

<table>
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<th>Table 2: complications of T1DM</th>
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<td><strong>Short term complications</strong></td>
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<td><strong>Long term complications</strong></td>
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<td><strong>Long term complications</strong></td>
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<td><strong>Macrovascular</strong></td>
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Another goal of T1DM treatment is to facilitate the patient in leading a life as normally as possible without limitations, or as few as possible, in daily activity. Good glycaemic control allows children to go to school without interruptions in their education due to their T1DM, and to participate in sports and other social activities to the same extent as children without T1DM.

Achieving good glycaemic control requires properly developed self-management skills, including a correct use of insulin with MDI or CSII, and frequent daily SMBG or rtCGM. Developing these complex and sophisticated self-management skills requires extensive and ongoing education, and a mutually trusting relationship between patients, parents, and medical team. Diabetes self-management will of course have to take into account differences between children of various ages and differences in understanding and (coping) possibilities of both patients and caregivers (32). Despite the critical importance of teaching and learning proper T1DM self-management skills for long-term glycaemic control, there is hardly any evidence on the key factors related to successful self-management education in diabetes.

Unfortunately, in daily practice, it is hard to achieve and maintain treatment goals as recommended in the ISPAD guidelines, especially during puberty (40). Administering insulin boluses and performing SMBG just before or during meals is particularly challenging in adolescents. Adolescents usually manage their T1DM increasingly independently, with waning supervision from their parents or caregivers. However, many adolescents lack the coping and problem-solving skills to adequately self-manage their disease, and poor adherence to insulin treatment is particularly common in this age range (42,43). Most children and adolescents with T1DM do not reach their HbA1c targets, especially adolescent girls with longstanding disease (44–46). Although it is generally assumed that adherence to insulin management is of key importance for the short- and long-term complication risk in T1DM and that poor adherence to insulin management is common in the paediatric age range, particularly in adolescents, the literature on the impact and the determinants of poor adherence in T1DM in children is surprisingly scant. In the few short-term studies available, insulin bolus frequency and SMBG frequency were determinants of HbA1c levels (47).

The management of T1DM is intensive and complex. Over the past decades, management of this disease has evolved from a ‘one-size fits all’ MDI approach to a patient-specific multidisciplinary team approach with many different insulin preparations for MDI, CSII, combined with either SMBG or CGM. With this complex, intensive and multidisciplinary care, the costs of treatment per child have increased significantly (41). Together with the increased T1DM prevalence in children, this will have considerable impact on the national healthcare budget needed to deliver appropriate care for these patients.
From a societal point of view, helping children and their parents to cope with T1DM self-management, will help to lessen the individual and family burden. Depending on the insurance system of a country, the costs involved in proper management and treatment of T1DM will be incurred by the community through health insurance, by the family itself, or a combination of these two. In the Netherlands, T1DM treatment costs are mainly borne by the community through universal health insurance.

Efforts to clearly demonstrate the financial impact of T1DM management in a country are quite often hampered by the restricted availability of data on costs and the need to obtain such information from a sometimes overwhelming array of data sources.

In the Netherlands, information of health reimbursement data is concentrated in the national healthcare information centre Vektis (48). Vektis was set up by health insurers to support claims reimbursement and enable the main stakeholders in Dutch healthcare to base their decision-making and policy execution on reliable, essential and timely data (48). This allows the assessment of information with regards to the majority of costs in children and adolescents with T1DM in the Netherlands. Information on personal and family expenses in relation to diabetes is more difficult to obtain.

**Aims of this thesis**

*Incidence and prevalence of T1DM in Dutch children*

During the last 25 years the prevalence of T1DM increased worldwide. In Europe, the increase in incidence rate appears to be 3-4% per annum with a variety in the rate of increase (7). Because recent data on the incidence of T1DM in Dutch children were lacking, the Vektis database was used to examine the prevalence and incidence of T1DM in Dutch children 0-14 years of age over several years (Chapter 2).

*Seasonality of diagnosis in children with type 1 diabetes mellitus*

The seasonality of many infectious diseases has been described in detail (49). Infectious diseases, which in part also have a seasonal distribution in their occurrence, are one of the most commonly mentioned possible triggers in the development of T1DM. Although seasonality of T1DM in different age groups has been examined (43,19), with most studies reporting a peak incidence in the autumn and winter (50,51), it is unknown whether and to what extent this phenomenon exists in the Netherlands. We therefore studied the seasonality of T1DM diagnosis in Dutch children (Chapter 3).

*Thyroid disease and type 1 diabetes mellitus*

Although the increased risk of autoimmune thyroid disease in children with T1DM is universally acknowledged, the scientific basis for this association is largely based on the demonstration of anti-thyroid antibodies in the blood of T1DM patients. Only about half of patients
with such anti-thyroid antibodies will develop overt autoimmune thyroid disease, and the incidence and prevalence of overt autoimmune hypo- and hyperthyroidism in children with T1DM are largely unknown. This was the topic of the study in Chapter 4.

*The overall health expenditure of a child with type 1 diabetes mellitus*

Studies on costs related to T1DM among children are scarce (52–54). Although the available literature suggests an increase in the T1DM-related costs over the last decades, no data are available on the costs of T1DM management for the Dutch healthcare system. *In Chapter 5*, both the overall healthcare costs in children with T1DM and the more specific costs related to the management of T1DM were investigated.

*Adherence to mealtime insulin bolusing and glycaemic control in adolescents on insulin pump therapy*

Poor self-management contributes to insufficient glycaemic control in adolescents with T1DM. However, studies examining the impact of poor adherence to CSII on medium- and long-term glycaemic control are rare in the paediatric age range, specifically in adolescents. *In Chapter 6*, we investigated the relation between adherence to mealtime boluses and SMBG with glycaemic control in adolescents.

*Factors related to optimal insulin pump management in adolescents with T1DM.*

In children with a chronic disease such as T1DM, nonadherence is common. Optimal management of T1DM improves both short-term glycaemic control and the prevention of long-term adverse sequelae. Factors underlying optimal adherence to self-management in CSII are largely unknown, however. *In Chapter 7*, we analysed the association of optimal adherence to CSII self-management in relation to age, gender, diabetes duration and the results of a number of questionnaires assessing the psychological and social consequences of T1DM filled out by patients and parents (including the Fear of self-testing questionnaire, Blood glucose monitoring communication questionnaire, the illness perception questionnaire (IPQ), the problem areas in diabetes (PAID–T) questionnaire, and the Diabetes family conflict scale).

A general discussion of the finding of these studies are is presented in *Chapter 8.*
Introduction

REFERENCES


Introduction


