

Virva Hannula

THE PREVALENCE OF
DIABETIC RETINOPATHY
AND ITS EFFECT ON SOCIAL
WELL-BEING AND HEALTH
RELATED QUALITY OF LIFE
IN CHILDREN AND YOUNG
ADULTS WITH
TYPE 1 DIABETES

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
OULU UNIVERSITY HOSPITAL



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Abstract

The incidence of childhood onset type 1 diabetes in Finland has been the highest in the world for several decades. Optimal management of the disease presents a lifelong challenge to the affected individuals. Related complications are common and include an ocular pathology called diabetic retinopathy. Type 1 diabetes with its ramifications can impact on several facets of a patient's physical and psychological well-being. This study aimed to assess the ophthalmic findings and to evaluate the characteristics of general well-being of a population-based cohort of paediatric patients with type 1 diabetes and a population-based cohort of young adults with type 1 diabetes since childhood.

The prevalence and risk factors of diabetic retinopathy were assessed of the population-based paediatric cohort in the catchment area of the Northern Ostrobothnia Hospital District and these were compared to a similar paediatric cohort studied 18 years previously. There was no significant change in the overall prevalence of diabetic retinopathy (12%) during the study period. Furthermore, glycaemic balance and other risk factors of diabetic retinopathy had remained almost unchanged.

A population-based cohort of young adults was evaluated in 2007 for the prevalence and severity of diabetic retinopathy. Most of the cohort subjects (94%) had developed diabetic retinopathy and in every third subject there was evidence of proliferative retinopathy. Health related quality of life was the same as that in the age- and gender-standardised control population. For the most part, the young adults with a long duration of type 1 diabetes fared equally well as the general population in the measured social aspects. However, proliferative diabetic retinopathy was associated with lower educational achievements and poorer health related quality of life as well as with a higher probability of unemployment or being pensioned.

Glycaemic balance and prevalence of diabetic retinopathy have remained unchanged in paediatric cohorts for nearly two decades despite concurrent advances in care. Social well-being was mainly restricted in young adults exhibiting signs of proliferative diabetic retinopathy. The negative impact of advanced complications of type 1 diabetes already in these young adults highlights the importance of strict metabolic control to maintain overall well-being.

Keywords: diabetic retinopathy, health related quality of life, prevalence, social well-being, type 1 diabetes

Hannula, Virva, Diabeettisen retinopatian esiintyminen ja vaikutus sosiaaliseen hyvinvointiin ja elämänlaatuun tyypin 1 diabetesta sairastavilla lapsilla ja nuorilla aikuisilla.

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Tiivistelmä

Lapsuusiässä alkavan tyypin 1 diabeteksen ilmaantuvuus on ollut Suomessa maailman korkein usean vuosikymmenen ajan. Hyvän hoitotasapainon ylläpitäminen on elinikäinen haaste sairastuneelle. Diabeteksen liitännäissairaudet ovat yleisiä, kuten myös silmänpohjissa todettava diabeettinen retinopatia. Tyypin 1 diabetes voi komplikaatioineen vaikuttaa laajasti potilaan fyysiseen ja psyykkiseen hyvinvointiin. Tässä tutkimuksessa pyrittiin arvioimaan silmien terveydentilaa ja yleiseen hyvinvointiin liittyviä tekijöitä tyypin 1 diabetesta sairastavien lasten sekä lapsena diabetekseen sairastuneiden nuorten aikuisten väestöpohjaisissa potilasaineistoissa.

Diabeettisen retinopatian esiintyvyys ja riskitekijät tutkittiin väestöpohjaisessa lapsipotilasaineistossa Pohjois-Pohjanmaan sairaanhoitopiirin alueella ja tuloksia verrattiin vastaavaan 18 vuotta aiemmin tutkittuun potilasaineistoon. Diabeettisen retinopatian esiintyvyys (12 %) ei ollut merkittävästi muuttunut tutkimusaikana. Glykeeminen tasapaino ja muut diabeettisen retinopatian riskitekijät olivat pysyneet kohorttien välillä oleellisilta osin ennallaan.

Lapsena sairastuneiden nuorten aikuisten väestöpohjaisesta potilasaineistosta arvioitiin diabeettisen retinopatian esiintyvyys ja vaikeusaste vuonna 2007. Enemmistölle potilaista (94 %) oli kehittynyt diabeettinen retinopatia ja kolmanneksella todettiin proliferatiivinen retinopatia. Terveysteen liittyvä elämänlaatu oli verrattavissa ikä- ja sukupuolivakioituun verrokki- väestöön. Sosiaalista hyvinvointia mittaavat tulokset olivat pääosin yhtäläiset muuhun väestöön verrattuna. Proliferatiivisella diabeettisella retinopatiolla havaittiin kuitenkin yhteys huonompaan terveyteen liittyvään elämänlaatuun ja koulutustasoon sekä korkeampiin työttömyys- ja eläköitymislukuihin.

Tutkitussa aineistossa lapsipotilaiden glykeeminen tasapaino sekä diabeettisen retinopatian esiintyvyys pysyivät ennallaan lähes kahden vuosikymmenen ajan hoitojen kehittymisestä huolimatta. Nuorten aikuisten sosiaalisessa hyvinvoinnissa esiintyi poikkeavuuksia lähinnä proliferatiivista diabeettista retinopatiaa sairastavilla. Tyypin 1 diabeteksen pitkälle edenneiden komplikaatioiden negatiivinen vaikutus jo nuorella aikuisiällä korostaa hyvän hoitotasapainon tärkeyttä yleisen elämänlaadun ylläpitämisessä.

Asiasanat: diabeettinen retinopatia, esiintyvyys, sosiaalinen hyvinvointi, terveyteen liittyvä elämänlaatu, tyypin 1 diabetes

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Virva Hannula

Abbreviations

ADA	American Diabetes Association
BCVA	Best corrected visual acuity
BP	Blood pressure
CSII	Continuous subcutaneous insulin infusion
CVD	Cardiovascular disease
DAWN	Diabetes Attitudes, Wishes and Needs study
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DR	Diabetic retinopathy
EDIC	Epidemiology of Diabetes Interventions and Complications
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FinnDiane	Finnish Diabetic Nephropathy Study
HbA1c	Haemoglobin A1c
HLA	Human leucocyte antigen
HRQoL	Health related quality of life
ICD	International Classification of Diseases
IOP	Intraocular pressure
MDI	Multiple daily injections
OCT	Optical coherence tomography
PDR	Proliferative diabetic retinopathy
QoL	Quality of life
T1D	Type 1 diabetes
T2D	Type 2 diabetes
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEP	Visual evoked potential
WDRS	Wisconsin Diabetes Registry Study
WESDR	Wisconsin epidemiologic study of diabetic retinopathy
WHO	World Health Organization

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals.

- I Kubin M, Tossavainen P, Hannula V, Lahti S, Hautala N, Falck A (2011) Prevalence of retinopathy in Finnish children and adolescents with type 1 diabetes: a cross-sectional population-based retrospective study. *Arch Dis Child* 96(10): 963–8.
- II Hannula V, Hautala N, Sintonen H, Falck A (2014) Health-related quality of life – using the 15D instrument – of young adults with type 1 diabetes since childhood. Population-based Oulu cohort study of diabetic retinopathy. *Acta Ophthalmol* 92(3): 205–8.
- III Hautala N, Hannula V, Palosaari T, Ebeling T, Falck A (2014) Prevalence of diabetic retinopathy in young adults with type 1 diabetes since childhood. The Oulu cohort study of diabetic retinopathy. *Acta Ophthalmol* 92(8): 749–52.
- IV Hannula V, Hautala N, Tossavainen P, Falck A (2015) Social well-being of young adults with type 1 diabetes since childhood. The Oulu cohort study of diabetic retinopathy. *Scand J Public Health* 43(6): 623–8.

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1 Introduction

Type 1 diabetes (T1D) is a severe chronic disease with no simple cure or proven means of prevention. It represents a growing burden on the finances of the healthcare system as well as being a considerable impediment in the lives of affected individuals. The overall incidence of T1D among children under 15 years of age has risen worldwide by approximately 3% annually for the past decades (Borchers *et al.* 2010, DIAMOND Project Group 2006, Patterson *et al.* 2012). T1D presents with marked geographical variations and for unclear reasons, Finland has the highest incidence in the world (Harjutsalo *et al.* 2008). Age at onset has shifted towards the youngest (0–4 years) children according to several European studies (Dahlquist & Mustonen 2000, Harjutsalo *et al.* 2008, Patterson *et al.* 2009).

In global terms, the incidence of T1D has increased since the mid-20th century (Dabelea 2009, Gale 2002). The incessantly rising incidence cannot be attributed to any single variable. Environmental factors are thought to be of major importance in view of the geographically uneven distribution of T1D and the relatively rapid increase in incidence (Hermann *et al.* 2003, Patterson *et al.* 2009). Extensive research is ongoing to identify the predisposing factors and chain of events leading to T1D onset. Among other possibilities, enterovirus infections in genetically susceptible individuals are currently speculated to have a role in the development of clinical T1D (Yeung *et al.* 2011).

A lifelong illness like T1D changes the patient's everyday routines permanently from the time of diagnosis. Crucial details about blood glucose self-monitoring, medications and nutrition need to be mastered. Daily behaviour is structured in a new way and especially at first, the complex treatment regimen may feel restricting and overwhelming. Maintaining an optimal glycaemic balance requires tenacious efforts and commitment to self-care. Even with meticulous treatment adherence, diabetic complications become more frequent as decades pass (Moore *et al.* 2009).

Diabetic retinopathy (DR) is a common microvascular complication of T1D along with diabetic nephropathy and neuropathy (Melendez-Ramirez *et al.* 2010). There are several modifiable and non-modifiable risk factors which determine if and when these complications will become manifest. DR is frequently symptomless until evolving into a severe vision-threatening form. It remains one of the leading causes of blindness among the working aged population in the developed countries (Congdon *et al.* 2003). Severe visual impairment can mostly

be avoided with prompt treatment. By attending systematic retinal screening, patients can ensure early detection and appropriately timed treatment of DR. A successfully executed chain of care should gradually reduce the prevalence and burden of DR induced visual impairment (Hautala *et al.* 2014a).

Neuroimaging studies have shown T1D to induce slight anatomical alterations in the structures of central nervous system, negatively affecting its functions (Northam *et al.* 2009, Sima 2010). Neuropsychological evaluations have associated T1D overtly with mild to moderate degrees of cognitive impairment (Brands *et al.* 2005). In particular, an early onset of T1D carries an increased risk for cognitive dysfunction (Gaudieri *et al.* 2008). Although the impairment in cognition is often regarded as clinically insignificant, it can become more evidently manifested in demanding situations (Brands *et al.* 2005). T1D related cognitive dysfunction can therefore impact in a negative manner on a susceptible individual's educational achievements and later opportunities concerning work and private life.

The majority of adolescents and young adults with T1D lead fairly ordinary lives. However, the disease with its associated complications and comorbidities may alter the quality of life (QoL) already at an early age (Graue *et al.* 2003, Kalyva *et al.* 2011). Psychosocial issues related to T1D are multifactorial and coping skills differ greatly between individuals. The disease demands permanent alterations in every patient's life and it may also affect life-changing choices made e.g. regarding education, work, relationships and family planning. These decisions have long-standing sequelae and they determine in part the social status of the individual.

Even though the incidence of T1D has increased in the past decades, there have been also significant positive advances made concerning the overall disease management. It is hoped that the improved care will translate into less severe and less prevalent DR among present-day children and young adults. This was the reason for comparing the prevalence of DR and its risk factors between two similar paediatric cohorts with T1D evaluated in 1989–1990 and 2007. In addition, a population-based cohort of young adults with T1D since childhood was evaluated in 2007 for the prevalence and severity of DR, health related quality of life (HRQoL) and social well-being.

2 Review of the literature

2.1 Type 1 diabetes

T1D accounts for about 5–15% of all cases of diabetes (ADA 2010, Diabetes: Current care guideline 2013). It is a complex lifelong illness with an onset most commonly during childhood or adolescence. The onset clusters typically at or near puberty (DIAMOND Project Group 2006, Pundziute-Lycka *et al.* 2002). A Finnish study found another peak in incidence at the age of five to seven years (Harjutsalo *et al.* 2008). No apparent gender difference has been detected in the occurrence of T1D, apart from a male preponderance from the age of 15 upwards (Gale & Gillespie 2001, Wandell & Carlsson 2013).

The treatment regimen for T1D consists essentially of exogenous insulin administration, carbohydrate intake counting and blood glucose monitoring (Diabetes: Current care guideline 2013). Additionally regular physical exercise is beneficial and highly recommended. The primary treatment goal focuses on maintaining the blood glucose level at normoglycaemic values in order to avoid or postpone the array of diabetic complications (DCCT Research Group 1994).

T1D is a multifactorial immune-mediated disease targeting the pancreas and terminating in the permanent loss of production of insulin (Noble 2015). Usually the disease onset is preceded by a latent pre-diabetic phase of variable length ranging from weeks to decades. At that time, single or multiple types of islet autoantibodies can be identified although there is no evidence of a clinical disease. The detection of a single T1D related autoantibody only seldom leads to clinical disease and occasionally the discovered seroconversion can also be transient (Knip *et al.* 2010, Yu *et al.* 2000). However, the detection of multiple autoantibodies increases substantially the risk of developing overt T1D (Kulmala *et al.* 1998, Pihoker *et al.* 2005, Ziegler *et al.* 2013).

According to three prospective birth cohort studies, 84% of children with multiple autoantibodies were diagnosed with T1D within 15 years from seroconversion (Ziegler *et al.* 2013). The progression rate to manifest T1D was particularly rapid when multiple autoantibodies were present before the age of three years (Ziegler *et al.* 2013). Some individuals will never develop T1D regardless of predisposing seropositivity and the number of autoantibodies. In those cases, successful immunoregulation is thought to have arrested the disease progression at an asymptomatic pre-clinical phase (Ziegler & Nepom 2010).

The actual destruction of the pancreatic islets is caused by a misdirected T cell response against the insulin producing β -cells. The plasma glucose level rises, leading to hyperglycaemia once the production of insulin has been critically compromised. It has been estimated that the pancreatic β -cell count needs to decline by approximately 80–90% before the clinical signs of T1D appear (Daaboul & Schatz 2003, Knip 1997). The long-term elevation of plasma glucose above the normal range is pathognomonic for T1D. At disease onset, patients often present quite acutely with fatigue, weight loss and signs of the classic triad of polyuria, polydipsia and polyphagia (Stipancic *et al.* 2011).

Diabetic ketoacidosis (DKA) is imminent when the diagnosis of overt T1D is delayed for any reason. DKA is caused by an accumulation of ketones in the body as alternate fuel sources need to be accessed in the absence of available glucose (Gosmanov *et al.* 2014). If no treatment is administered, DKA is ultimately followed by diabetic coma and death. Estimates of the frequency of DKA at the time of T1D diagnosis vary extensively, ranging from 13% to 80% (Usher-Smith *et al.* 2012). In Finland, a fairly recent study reported a 19% frequency of DKA at T1D onset (Hekkala *et al.* 2010). The risk of DKA remains especially high among children under two years of age (Oyarzabal Irigoyen *et al.* 2012, Schober *et al.* 2010). In countries with a low prevalence of T1D, the diagnosis may be more commonly delayed due to the rarity of the condition.

T1D can be adequately controlled with the methods of modern healthcare. Nevertheless, the body's endocrine regulatory mechanisms are difficult to replicate and the daily management of T1D requires a firm commitment from the patient. Despite his/her best efforts, the course of the disease often leads to various impairments in different tissues. Thus far, trials searching for a preventive measure to inhibit the development of overt T1D have not been successful (Skyler 2013).

2.1.1 History of type 1 diabetes

T1D, earlier referred to as childhood diabetes, was a well-known but rare disease around the turn of the 20th century. The treatment of choice in the Naunyn era (1898–1914) was a nutritional regimen strictly avoiding carbohydrates (Ney & Hollingsworth 1981, Sherrill 1953). The recommended diet was rich in fat and protein which were often prescribed to the point of nausea. The following Allen era (1914–1921) focused on limiting calorie intake to near or overt starvation (e.g. 26 cal/kg) which succeeded in only slightly prolonging the patients' lives (Allen

et al. 1919, Ney & Hollingsworth 1981). Before effective treatment was available, the life expectancy of a child after diabetes diagnosis was at best one to two years (Gale 2002, Marks 1965).

A tremendous breakthrough in diabetes care was achieved in the University of Toronto in 1921 when a young Canadian physician, Frederick Banting, and his assisting medical student, Charles Best, discovered insulin (Rosenfeld 2002, Roth *et al.* 2012). Closely associated with the discovery were also the head of physiology at the University of Toronto, Professor John MacLeod, and biochemist James Collip, who succeeded in the purification of insulin.

The first human patient, a 14-year old boy about to die of diabetes, was successfully treated with exogenous insulin in 1922 (Banting *et al.* 1991). Childhood diabetes was transformed from a death sentence to a treatable condition with the rapidly commencing commercial production of insulin. Banting and Macleod were jointly awarded Nobel Prize in Physiology or Medicine in 1923 for their lifesaving discovery.

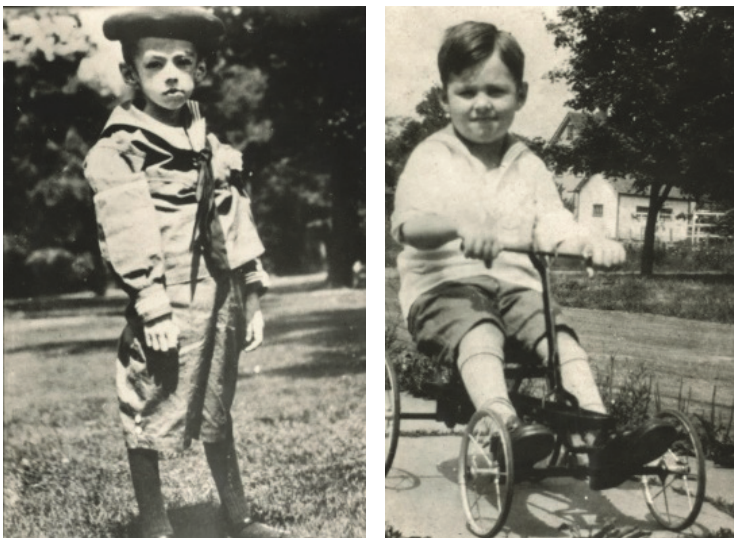


Fig. 1. Five-year-old Theodore Ryder was one of the first patients to receive insulin. Pictures show his transformation after the administration of exogenous insulin.

Several diabetes-related complications had already been recognised during the pre-insulin era. However, long-term complications became fully evident only after the introduction of insulin therapy and the subsequent increase in patients'

life expectancies. At first, insulin therapy was fairly rudimentary and extensive glycaemic fluctuations led to the rapid development of a variety of diabetic complications. With greatly improved treatment modalities, the life expectancy of the T1D population has increased significantly in the post-insulin era (Miller *et al.* 2012).

The past decades have seen important developments facilitating efficient self-management, contributing to accurate glucose monitoring and increasing the ease of care. These factors have brought the life expectancy of the T1D population substantially closer to their non-diabetic counterparts. Despite major improvements in care, T1D is still associated with increased mortality, mostly due to long-term diabetic complications (Harjutsalo *et al.* 2011, Jorgensen *et al.* 2013, Skrivarhaug *et al.* 2006a). The unfavourable prognosis of severe renal complications have been particularly well documented. Accordingly, some studies have detected equal mortality if the T1D population with normoalbuminuria is compared to the general population (Groop *et al.* 2009, Orchard *et al.* 2010).

An excess mortality rate has been observed even in young T1D patients with a relatively short duration of the disease and before developing late diabetic complications (Dahlquist & Kallen 2005, Podar *et al.* 2000). At young ages, the most frequent diabetes-related cause of death is DKA. In addition, a noteworthy number of unexplained deaths during sleep are recorded with autopsies detecting no apparent cause of death (Dahlquist & Kallen 2005, Sartor & Dahlquist 1995, Tattersall & Gill 1991). These sudden deaths, also known as dead in bed-syndrome, are thought to result from nocturnal hypoglycaemia (Tanenberg *et al.* 2010). They have been estimated to be responsible for 6% of all deaths in diabetic patients aged <40 years (Sovik & Thordarson 1999).

T1D management has undergone radical changes during the past century (Giani *et al.* 2015). The indisputable breakthrough in the history of T1D was the introduction of insulin replacement therapy. At first, the commercially produced insulin was extracted primarily from pigs and cows until in the early 1980s, synthetic human insulin was developed. Nowadays insulin analogues are manufactured with highly precise therapeutic effects. Other significant technological advances have led e.g. to the use of insulin syringes, prefilled insulin pens, continuous subcutaneous insulin infusion (CSII) devices and self-monitoring blood glucose meters. The development of glycated haemoglobin A1c (HbA1c) measurement has allowed more accurate long-term assessment of glycaemic balance and adjustment to care.

Modifiable risk factor management, patient education and treatment guidelines have undergone significant improvements. Since around the 1980s, there was a change away from insulin administration one or twice a day to multiple daily injections (MDI) or CSII. These advances made a clear difference in the patient's ability to achieve blood glucose levels closer to normoglycemia. The benefits of current standard of care have been well established in large studies including Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) (DCCT Research Group 1993, Nathan & DCCT/EDIC Research Group 2014).

2.1.2 Genetics of type 1 diabetes

The onset of T1D is preceded by a combinative interplay between genetically predisposing factors and environmental triggers. The importance of genetics in the aetiology of T1D is evident from twin studies which have found a significantly higher concordance of the disease in monozygotic twins than in dizygotic twins (Kumar *et al.* 1993, Kyvik *et al.* 1995). The remaining discordance in the monozygotic twins confirms the influence of unshared environmental factors in T1D development (Kyvik *et al.* 1995). The incidence rate of T1D has a distinctly irregular geographical distribution and this is thought to be largely due to differences in exposure to environmental factors.

At present, the genetic risk factors of T1D are more thoroughly understood than the environmental triggers. Genes in the human leucocyte antigen (HLA) region at 6p21 are the main contributors to an individual's genetic susceptibility to the disease accounting for about 40–50% of the genetic risk for T1D (Baker & Steck 2011, Xie *et al.* 2014). However, the polygenicity of T1D is well documented and there are numerous other genes of lesser importance outside the main HLA complex.

The inheritance of T1D may raise concerns especially during family planning or after an unexpected T1D diagnosis in a family (van Esch *et al.* 2010). Predisposing genes are common in the general population. However, in most cases the inheritance pattern of T1D is rather weak and currently the importance of genetic predisposition has further declined due to strong environmental pressure. Only a minority (<10%) of all genetically susceptible individuals will develop the disease (Knip *et al.* 2005, Tuomilehto 2013).

The risk of developing T1D has been often cited at 0.4% in the general population (Runge & Patterson 2007, Wass & Stewart 2011). The existence of an

affected first degree relative confers an increased genetic risk for developing the disease. Men are more likely to transfer T1D to their offspring than women (Gale & Gillespie 2001, Tuomilehto *et al.* 1995). According to a Finnish study, a child's risk of acquiring T1D from an affected mother is 5% compared to 8% from a father with T1D (Harjutsalo *et al.* 2006). Siblings of a child with T1D have on average 6% cumulative incidence of developing T1D by the age of 30 years (Harjutsalo *et al.* 2005, Lorenzen *et al.* 1994). An individual's risk of T1D increases to 20% with HLA-conferred susceptibility to the disease and several affected first degree relatives (Bonifacio *et al.* 2004).

A subject's risk of developing T1D can be more individually evaluated with assessment of T1D related HLA risk alleles, autoantibodies and the first-phase insulin response in glucose tolerance test (Diabetes: Current care guideline 2013, Siljander *et al.* 2013). However, individuals with mild or even a protective genetic predisposition to T1D are increasingly often developing T1D as the importance of high risk genotypes has declined over time (Borchers *et al.* 2010, Hermann *et al.* 2003). Nowadays, the new cases of T1D are often sporadic with the diagnosed patient being the only affected one in the family. Only approximately 10–20% of newly diagnosed patients have a first-degree relative with T1D (Dahlquist *et al.* 1985, Larsson *et al.* 2004, Tuomilehto 2013).

2.1.3 Epidemiology and prevalence of type 1 diabetes

During the past century, T1D was transformed from a deadly and rare disease to a high prevalence chronic condition. The incidence of T1D has grown predominantly in a continuous linear manner since the mid-20th century (Dabelea 2009, Gale 2002, Krolewski *et al.* 1987). This change has not occurred uniformly and substantial differences in incidence rates can be seen between nations as well as between specific geographic areas. Lately the incidence of T1D has increased by approximately 3–4% annually in most European countries (Patterson *et al.* 2012). The incidence of T1D in Finland is now approximately five times greater than it was 60 years ago, with the steepest increase rates being recorded in the most recent decades (Tuomilehto 2013).

The reasons for the rapid increase in the incidence of T1D are not fully understood. The vastly improved prognosis after the discovery of insulin allowed patients to reach reproductive age. However, the increase in incidence has been too rapid to be explained primarily by changes in genetics (Hermann *et al.* 2003, Patterson *et al.* 2009). The rapidly rising incidence combined with the extensive

geographical heterogeneity of T1D emphasize the crucial role of environmental factors in the upsurge of the disease. These undefined exogenous triggers have become increasingly important in the development of T1D. Accordingly, individuals relocating from low-incidence populations can experience a rise in the incidence rate of T1D after moving to a high-incidence location (Bodansky *et al.* 1992).

The age at T1D onset has shifted towards younger children in several countries with the largest increases in incidence rates often being reported among 0–4 year-olds (EURODIAB ACE Study Group 2000, Harjutsalo *et al.* 2008, Patterson *et al.* 2009, Patterson *et al.* 2014). In the past decades, the incidence of childhood onset T1D (0–14 years) in Finland has been by far the highest of any country (DIAMOND Project Group 2006, EURODIAB ACE Study Group 2000). The current peak was registered in 2006 when the incidence of T1D climbed to 65 per 100 000 (Harjutsalo *et al.* 2013).

According to global estimates, the incidence of childhood onset T1D varies by approximately 600-fold, from the lowest values in Venezuela (0.1 per 100 000) to the highest in Finland (57.6 per 100 000) (IDF Diabetes Atlas 2013). There are extensive geographic differences in T1D incidence and prevalence, even taking into account discrepancies in data accuracy and availability between countries (Patterson *et al.* 2014). Interestingly, several low-prevalence countries are currently experiencing some of the steepest increases in incidence rates (Patterson *et al.* 2009).

In the 1990s, the incidence of T1D in Finland was over three times greater than that in neighbouring Estonia, despite the geographical proximity of the two countries (Podar *et al.* 2001). Similarly, a nearly six-fold gradient in the incidence of T1D was detected in the comparison between Finland with the adjacent Russian Karelia (Kondrashova *et al.* 2005). The predisposing HLA-DQ genotypes were equally often detected in both background populations. On both sides of the border, the non-diabetic schoolchildren had a similar frequency of β -cell autoimmunity, differing only in the progressive form of autoimmunity associated with late pre-clinical phase of T1D (Kondrashova *et al.* 2007). These findings indicate that the strong environmental exposure in Finland leads exceptionally often to the development of overt T1D.

Recently there has been some indication that a plateau has been reached in the incidence of T1D among Finnish children (Harjutsalo *et al.* 2013). Similar promising results have been reported from Sweden (Berhan *et al.* 2011), Norway (Skrivarhaug *et al.* 2014) and the Czech Republic (Cinek *et al.* 2012). Further

evidence will be needed to confirm the long-awaited arrest in the incessantly rising incidence of T1D.

Intensive research is ongoing in attempts to clarify the disease pathology and development. For example, the effects of early infant diet, excessive hygiene, toxins and vitamin D deficiency have been widely studied (Heikkinen *et al.* 2013, Hettiarachchi *et al.* 2008, Ziegler *et al.* 2003, Zipitis & Akobeng 2008). In addition, the possibility of a lost protective factor has been considered. Some promising advances have been made in recent years linking enterovirus infections to the development of pancreatic islet autoantibodies and overt T1D (Laitinen *et al.* 2014, Yeung *et al.* 2011).

A north-south gradient has been detected in incidence rates of T1D, especially in European studies. Higher incidence rates in Europe are situated in northerly countries and lower in southerly, although high-incidence Sardinia represents one exception (EURODIAB ACE Study Group 2000). Some studies support a seasonality of T1D manifestation, with the clinical onset peaking during wintertime (Green *et al.* 2001, Levy-Marchal *et al.* 1995). During colder months, several viral infections are more prevalent and this might support the theory that viral infections can influence the disease onset. Seasonal variations on the frequency of T1D diagnosis are most evident in countries with clear differences between warmer and colder seasons. Less conclusive data is available with regard to the effect of seasonality of birth (Soltesz *et al.* 2007).

2.1.4 Metabolic memory

During 1983–1993, the DCCT research group established that intensive treatment was beneficial in delaying the onset and progression of T1D related complications in comparison to conventional treatment (DCCT Research Group 1993). The intensive treatment consisted of three or more daily insulin injections or corresponding CSII therapy with the object of having glucose levels as close to normoglycemia as safely possible. The conventional treatment group complied with the standard care of the 1980s with one or two insulin injections per day aimed at avoiding the clinical symptoms of hypoglycaemia and hyperglycaemia (The DCCT Research Group 1986).

Intensive treatment proved to be highly beneficial during the course of the study. In 1994, the completed DCCT study was continued under the name of EDIC, a long-term observational follow-up study with over 90% participation from the original DCCT cohort. The former treatment groups were both advised

to adhere to intensive treatment and all study subjects returned to their original healthcare providers. The focus of the study shifted to the sustainability of the effects of original DCCT study, especially in relation to more advanced diabetic complications (The EDIC Research Group 1999).

With the entire EDIC study population instructed to comply with the intensive treatment regimen, the glycaemic differences between former groups diminished and later disappeared (Nathan & DCCT/EDIC Research Group 2014). However, a clear disparity in the frequency of diabetic complications remained between the groups regardless of the fact that the subjects gradually achieved glycaemic concordance. The mean 6.5 years of intensive glycaemic control during DCCT had resulted in a long-term benefit, reducing significantly the frequency of diabetic complications. This unexpected phenomenon was termed metabolic memory. During the subsequent 18-year follow-up, the protective effect has weakened but thus far not disappeared (Gubitosi-Klug & DCCT/EDIC Research Group 2014).

The legacy of intensive glycaemic control strongly advocates rapid introduction of well-tailored insulin replacement therapy as soon as possible after T1D diagnosis. Adherence to strict glycaemic balance can substantially delay several T1D related micro- and macrovascular complications and even prevent their occurrences. In addition, the positive outcomes of intensive treatment help to maintain a favourable HRQoL (Jacobson *et al.* 2013). The EDIC study is still ongoing and more long-term data can be expected in the future.

2.1.5 Microvascular complications of type 1 diabetes

T1D is associated with microvascular complications i.e. diabetic retinopathy, neuropathy and nephropathy. Hyperglycaemia is a major risk factor for all of the above conditions (Diabetes: Current care guideline 2013). Microvascular complications can be delayed or sometimes prevented with good metabolic control and overall successful management of T1D (DCCT Research Group 1993). Some patients remain free from all or some diabetic complications even with T1D of extreme duration. A study examining patients who had been diagnosed with T1D over 50 years previously found high percentages of subjects free from PDR (43%), nephropathy (87%), neuropathy (39%) and cardiovascular disease (52%). No association to glycaemic control was found and those subjects were speculated to be benefitting from unknown endogenous protective factors (Sun *et al.* 2011).

The majority of the morbidity and mortality related to T1D results from both microvascular and macrovascular diabetic complications (Daneman 2006). The controls performed at diabetes clinics include regular screening tests for microvascular complications: laboratory tests are conducted to monitor kidney function, feet are evaluated for protective sensation and fundus photographs are assessed to detect DR.

Diabetic retinopathy will be more thoroughly described in chapter 2.2.

Diabetic nephropathy

The first clinical sign of T1D related renal deficiency is microalbuminuria. Small albumin proteins are able to pass into the glomerular filtrate and they are secreted into urine at a rate of 20–200µg/min. A significant percentage of microalbuminuric individuals can revert back to normoalbuminuria (de Boer *et al.* 2011, Giorgino *et al.* 2004, Perkins *et al.* 2003). However, approximately 30% of patients develop persistent microalbuminuria within the first 20 years after the diagnosis of T1D (Hovind *et al.* 2004). If glomerular damage accumulates, irreversible renal changes may occur leading to macroalbuminuria with albumin secretion of >200µg/min. The excess mortality related to T1D is largely due to diabetic nephropathy (Jorgensen *et al.* 2013).

Diabetic neuropathy

T1D induced damage to the nerve fibres is referred to as diabetic neuropathy. It can affect any nerve throughout the body and have a wide range of clinical manifestations such as focal, autonomic, proximal or peripheral neuropathy. Focal neuropathy affects specific nerve sites and the outcome is often transient e.g. diplopia due to cranial nerve lesion or facial paralysis in Bell's palsy. Autonomic neuropathy may damage several organ systems e.g. it can induce cardiovascular dysfunction, hypoglycaemia unawareness and exercise intolerance. In its advanced form, autonomic neuropathy can have detrimental consequences and it has been associated with the dead in bed-syndrome (Tang *et al.* 2013). Proximal neuropathy often causes lower-extremity weakness and pain. Peripheral neuropathy may lead to decreased protective sensation and a high risk of developing foot ulcers. There is no cure for diabetic neuropathy once it has become established but symptoms can often be controlled. The successful management of T1D can prevent occurrences.

2.1.6 Macrovascular complications of type 1 diabetes

Macrovascular complications of T1D are related to advancing atherosclerosis as large blood vessels are damaged by the persistent exposure to hyperglycaemia. The inner lining of blood vessels thickens and the lumen diameter decreases, diminishing blood flow. A complex cascade involving an inflammatory component predisposes to cardiovascular events including coronary artery disease, peripheral arterial disease and stroke. These may be delayed or prevented by intensive treatment of diabetes (Lachin *et al.* 2014, Nathan *et al.* 2005).

The risk of developing cardiovascular disease (CVD) is substantially higher for individuals with T1D compared to the non-diabetic population (Laing *et al.* 2003). Major modifiable risk factors for CVD include high blood pressure (BP), smoking and hyperlipidaemia. In addition, an elevation of HbA1c value by one unit (%) was assessed to increase CVD mortality by 53% among the Finnish population with late onset T1D (Juutilainen *et al.* 2008).

2.1.7 Cognitive impairment related to type 1 diabetes

Glucose is virtually the sole source of energy for brain tissue under normal cerebral functioning. The lack of storage capabilities makes brain cells especially dependent on a steady supply of glucose from the blood circulation (Moheet *et al.* 2015, Seaquist 2015). T1D frequently causes abnormal fluctuations in the glucose level. Hypoglycaemic episodes and perhaps also recurrent hyperglycaemia have been strongly suspected of causing various structural and functional deficits, particularly in the immature brain (Lin *et al.* 2010, Perantie *et al.* 2008, Ryan & Becker 1999).

T1D has been indisputably associated with a risk of developing cognitive impairments (Brands *et al.* 2005, McCrimmon *et al.* 2012). Neuroimaging has revealed specific structural alterations in the brain anatomy of patients with T1D (Musen 2008, Stiles & Seaquist 2010). Neuropsychological tests have revealed that patients with T1D have a slightly poorer neurocognitive performance across most cognitive domains including intelligence, processing speed, executive function and attention (Gaudieri *et al.* 2008, Northam *et al.* 2001). A meta-analysis of the neuropsychological performance of paediatric patients concluded that children with T1D seemed to suffer from subtle cognitive impairments and they had mildly reduced intellectual quotients when compared to non-diabetic children (Naguib *et al.* 2009).

Some neuropsychological evaluations have considered T1D induced deficits in cognition to be predominantly mild and clinically insignificant (Biessels *et al.* 2007). However, several studies have claimed that paediatric patients with early onset of T1D (<5–7 years) appear to be especially susceptible to cognitive deficits (Biessels *et al.* 2007, Desrocher & Rovet 2004, Gaudieri *et al.* 2008). Children with early-onset of T1D are prone to experience minor learning difficulties during their early school years (Hannonen *et al.* 2010). The overall academic performance of pupils with early onset of the disease has been estimated to be slightly poorer than their peers with later disease onset (Gaudieri *et al.* 2008). Mild central brain atrophy has been detected in adults with early-onset T1D (Ferguson *et al.* 2005). In addition, a corresponding decline in intellectual performance was recorded when comparing the early-onset adults to a similar group with later onset of T1D (Ferguson *et al.* 2005).

On average, adolescents and young adults with T1D manage their lives without excessive difficulties. However, even minor cognitive deficits may hinder an individual's performance in challenging situations (Brands *et al.* 2005). The potential negative effect could impact on social opportunities e.g. concerning education or worklife. The adverse effect of T1D on the developing brain is especially significant as the age of onset has shifted towards younger children. With the growing incidence of T1D, an increasing number of young paediatric patients will be affected by the disadvantageous cognitive prognosis.

2.1.8 Social benefits related to type 1 diabetes in Finland

In Finland, patients with T1D form a large group of approximately 50 000 individuals (Diabetes: Current care guideline 2013). Since Finland has the highest incidence of T1D of any country, the national cost of care is substantial. Finland has long strived to provide equal access to high quality healthcare regardless of the patient's financial status or other means. In 1964, an important milestone was reached with the Health Insurance Act lowering the cost to the patient of various healthcare needs (Finlex 2004). This covers all permanent residents of Finland and is designed to reduce the cost of medical examinations and treatments, medications and illness-related transportations etc. It also compensates for loss of income due to incapacity for work.

In accordance with the Health Insurance Act in 1964, Finland implemented a medicine reimbursement system. This grants predetermined reimbursements for certain prescription medication costs according to the severity of the illness and

necessity of the medication (Fimea & Social insurance institution 2013). Each patient with diagnosed T1D is eligible for reimbursements and is added to the Social Insurance Institution's entitlement register.

All insulin preparations and oral medications for lowering blood glucose are included in the higher special refund category and are therefore fully reimbursed excluding currently a non-reimbursable sum of three euros for each purchased medicine. The refund is usually credited directly at the time of purchase. The other medications that an individual with T1D might need e.g. for treating hyperlipidaemia or hypertension, are reimbursed according to their respective refund category.

Since 1972, the Primary Health Care Act, revised as the Health Care Act in 2011, has guaranteed free care-equipment supply for T1D patients (Finlex 2010). At present, insulin pens and needles, materials for CSII, blood glucose meters and test strips are dispensed from healthcare centres according to each individual's needs. Social support for T1D population in Finland has also been extended to cover various disability benefits. Children under 16 years of age with T1D are entitled to a monthly disability allowance to compensate for the financial strain caused by T1D care. Older patients may also be eligible for other disability benefits according to their individual circumstances.

2.1.9 Cost of type 1 diabetes

T1D continues to be a significant public health issue with a high burden of care (Chevreul *et al.* 2014, Kruger & Brennan 2013). Its financial ramifications are felt by individual patients as well as national health economies, especially in countries with a high prevalence of T1D. The chronic disease generates substantial direct costs throughout an individual's lifespan and additional indirect costs e.g. related to disability, work loss and premature mortality.

The growing use of CSII devices, the introduction of insulin analogues and more frequent self-monitoring of blood glucose are among the factors responsible for increased T1D related health costs. In Germany, the main direct costs for adolescents with early onset of T1D were derived from glucose self-monitoring (29%), CSII therapy (25%), hospitalization (22%) and insulin (18%) (Bachle *et al.* 2013). Female gender, pubertal age and poor glycaemic control were associated with a higher total cost of T1D. The average cost per paediatric patient with T1D increased by 20% and the total cost for paediatric diabetes care by 47% during the period 2000–2007 in Germany (Bachle *et al.* 2012). The expansion of

direct costs of paediatric T1D care was partly attributed to the rising prevalence of T1D and to new therapeutic strategies.

Direct medical costs attributable to diabetes can vary considerably according to the age of the patient (Wirehn *et al.* 2008). In a Swedish population with unspecified diabetes, the direct healthcare cost was 1.8 times higher per person compared to the non-diabetic population. In children, the cost was 7.7 times higher and in patients aged >75 years 1.3 times higher than in the non-diabetic population (Wirehn *et al.* 2008). The difference in expenditure likely decreases with advancing age because the prevalence of serious health problems increases also among the non-diabetic population. Emerging complications and comorbidities of T1D accelerate the deterioration of physical health and HRQoL. The changes are likely to increase productivity losses and medical resource consumption, contributing to the overall economic burden of the disease. Treatment of T1D is imperative for sustaining life and therefore in Finland the financial strain for the patient is kept to a minimum.

Diabetic complications can be significantly more costly to manage than the underlying disease (Koster *et al.* 2006, Lesniowska *et al.* 2014). A substantial proportion of the direct and possibly also indirect diabetes-related costs originate from diabetic complications (Hex *et al.* 2012, Lesniowska *et al.* 2014, von Ferber *et al.* 2007). Reputedly, the cost of T1D treatment increases especially as diabetic nephropathy advances (Lithovius *et al.* 2013). In Finland, the cumulative cost of prescription medications for a T1D outpatient cohort was evaluated during 1998–2008 and patients with end-stage renal disease were found to generate major additional expenditures which increased by fourfold the medication costs (Lithovius *et al.* 2011).

The prolonged life expectancy in the T1D population adds to the total health resource expenditure. Increased longevity means an increase in the total number of utilized routine healthcare services. A long duration of T1D is commonly accompanied by micro- and macrovascular complications and advancing disease may necessitate more frequent assessments. Current care can significantly prolong the lives of even those patients with very advanced stages of the disease, likely increasing the total costs of medications and treatments.

2.2 Diabetic retinopathy

Before the mid-19th century, a French ophthalmologist, Appolinaire Bouchardat, noted that some patients with diabetes suffered from significant visual

impairment. No sign of cataract was detected but the symptoms responded favourably to improved glucose management (Bouchardat 1846). However, the link between diabetes and suspected ophthalmic pathology remained elusive until the invention of ophthalmoscopy. In 1855, the Austrian ophthalmologist, Eduard Jäger, was the first to describe in detail the diabetic macular changes (Jaeger 1870). Nevertheless, the connection between retinal findings and diabetes remained somewhat controversial in the scientific community well into the 20th century.

Nowadays DR is well known as a potentially sight-threatening complication of T1D (Virk *et al.* 2015). It is often the first microvascular complication to appear and accordingly some stage of DR is commonly detected in adults with T1D. The retina, the light sensitive tissue lining the back of the eye, undergoes structural changes as blood vessels become progressively damaged due to exposure to hyperglycaemia (Keel *et al.* 2014). The speed of the process varies according to several predisposing factors (DCCT Research Group 1993, DCCT/EDIC Research Group 2000, White *et al.* 2010). Usually both eyes are affected, but the stage of DR is not necessarily symmetrical. Ocular perfusion problems due to carotid artery disease might be suspected if the level of fundus pathology is very asymmetrical between the eyes (AAO 2015).

Once DR is present, its severity can vary from minimal non-proliferative changes to florid PDR. The prevalence of DR becomes almost universal with a long duration of T1D (LeCaire *et al.* 2013). Visual impairment related to T1D is usually caused by PDR and less frequently by diabetic maculopathy (Jeppesen & Bek 2004, Klein *et al.* 2010). DR may induce very little visual disturbance even in an advanced form, but then rapidly evoke a severe visual loss or blindness after reaching a critical point. However, with regular ophthalmic monitoring and timely interventions, DR can be managed in most cases without significant visual impairment (Diabetic retinopathy: Current care guideline 2014).

2.2.1 Pathogenesis of diabetic retinopathy

Unsatisfactory glycaemic balance is a fundamental contributor to the pathophysiology of DR (Keel *et al.* 2014). With time, hyperglycaemia causes the retinal vasculature to suffer a progressive dysfunction. The exact details to explain the pathogenesis of DR are not fully understood, although several interconnecting biochemical pathways are suspected to influence the development and progression of DR (Semeraro *et al.* 2015). These include increased activity of

the polyol pathway, activation of protein kinase C, increased expression of growth factors (e.g. vascular endothelial growth factors (VEGF) and insulin growth factors), hemodynamic changes, accelerated formation of advanced glycation end-products, oxidative stress, activation of the renin-angiotensin-aldosterone system, and subclinical inflammation and capillary occlusion (Tarr *et al.* 2013).

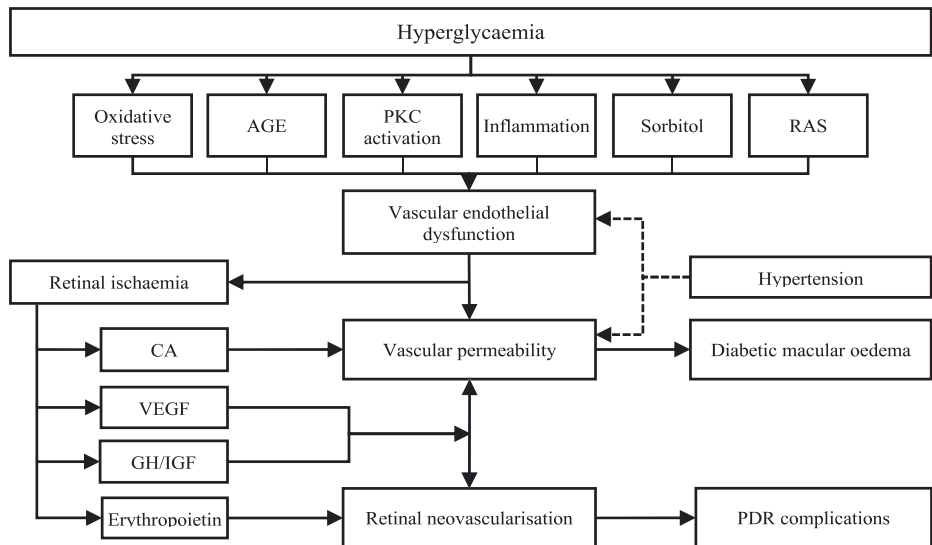


Fig. 2. Pathophysiology of diabetic retinopathy. Hyperglycaemia activates a cascade of events leading to retinal vascular endothelial dysfunction. The resultant retinal ischaemia and increased vascular permeability, augmented by hypertension, are two key common pathways underlying the development of vision-threatening diabetic retinopathy. AGE=advanced glycation end-products, PKC=protein kinase C, RAS=renin-angiotensin system, CA=carbonic anhydrase, GH/IGF=growth hormone/insulin growth factor. Modified from Cheung *et al.* 2010.

Long-term hyperglycaemia damages the endothelial cells in the retinal blood vessels. Thickening of the capillary basement membrane and the loss of intramural pericytes have been observed early in the course of the disease (Beltramo & Porta 2013, Gardiner *et al.* 2007, Mizutani *et al.* 1996). Endothelial cell loss, capillary occlusion and retinal hypoxia appear as the structural alterations advance. Several biochemical and anatomical changes can be detected as part of the compensatory mechanisms including elevated levels of

proangiogenic growth factors, venous calibre irregularities and intraretinal microvascular abnormalities (IRMA). When the integrity of the inner blood-retinal barrier is compromised, vascular permeability increases causing retinal oedema.

The retina has a high metabolic activity and cumulative vascular damage may leave extended areas of retina hypoperfused (AAO 2015). Ischemic changes and their magnitude can be assessed in detail with fluorescein angiography (FA). When a critical threshold of ischemia is reached, endothelial cells deprived of proliferation control may induce neovascular growth to compensate for hypoperfusion. The fragile new blood vessels start to grow on the retina or optic disc, resulting in overt PDR.

2.2.2 Prevalence of diabetic retinopathy

DR is fairly uncommon during the first three to five years after the onset of T1D and before puberty (Falck *et al.* 1993). The duration of T1D, both prepubertal and postpubertal years, is reflected in the time of DR onset. The years after puberty have a stronger impact and contribute twice as much to the development of DR than the years before puberty (Olsen *et al.* 2004). Microaneurysms are usually the first clinical sign of DR and the initial detection is often based on retinal screening images.

The duration of T1D quite accurately predicts the presence of DR. The probability of diabetic changes occurring in the fundus increases with the post-diagnosis time such that after 20 years, some degree of DR will be rather universally detected (LeCaire *et al.* 2013). The Wisconsin epidemiologic study of diabetic retinopathy (WESDR) reported some stage of DR in 17% and 98% of T1D patients after <5 and ≥ 15 years following diagnosis, respectively (Klein *et al.* 1984). With intensified glycaemic control and other significant advances in T1D care, several studies have detected a corresponding improvement in DR prevalence among adolescents (Downie *et al.* 2011, Mohsin *et al.* 2005).

The Wisconsin Diabetes Registry Study (WDRS) cohort, similar to WESDR but diagnosed on average two decades later, was compared to the original WESDR population. Although DR was common after 20 years of T1D in both cohorts, DR was less prevalent (92% in WDRS vs. 97% in WESDR) and less severe in the more recent WDRS cohort (LeCaire *et al.* 2013). An improved ophthalmic outcome over time was detected also within the WESDR population. More recently diagnosed cohorts had a lower prevalence of PDR despite similar

durations of T1D and independent of HbA1c, BP and the presence of proteinuria (Klein *et al.* 2008).

Several studies have detected a declining cumulative incidence of severe DR over the past decades. Although most current studies have reported a decreasing trend, the incidence rates display considerable variations. After 20–25 years of T1D duration, the cumulative incidence of severe DR or PDR varied between 6–13% in three Scandinavian countries (Hovind *et al.* 2003, Kyto *et al.* 2011, Skrivarhaug *et al.* 2006b). In comparison, the 25-year cumulative incidence of PDR was 42–43% in two other population-based cohorts (Grauslund *et al.* 2009b, Klein *et al.* 2008).

2.2.3 Classification of diabetic retinopathy

The time of DR onset and the severity of its manifestation vary significantly between individuals according to the presence of multiple protective and predisposing factors. The severity of DR can be broadly divided into three stages based on diabetic fundus changes; non-proliferative DR, pre-proliferative DR and PDR. In addition, diabetic maculopathy may appear at any stage of DR (Diabetic retinopathy: Current care guideline 2014).

The Finnish Current care guideline recommends DR to be classified for screening purposes according to the proposed international clinical classification system (Wilkinson *et al.* 2003). This consists of five stages of disease severity starting from no apparent retinal changes to PDR.

Table 1. Comparison of common classifications of DR. Detailed screening classification on page 72.

Screening classification	International classification	Status of retina
No DR	No DR	Normal fundus
Mild non-proliferative DR	Non-proliferative DR	Microaneurysms, haemorrhages, microinfarctions, lipid deposits, IRMA, venous beading
Moderate non-proliferative DR	Non-proliferative DR	Microaneurysms, haemorrhages, microinfarctions, lipid deposits, IRMA, venous beading
Severe non-proliferative DR	Pre-proliferative DR	4-2-1 rule (see page 37)
PDR	PDR	Neovascular growth

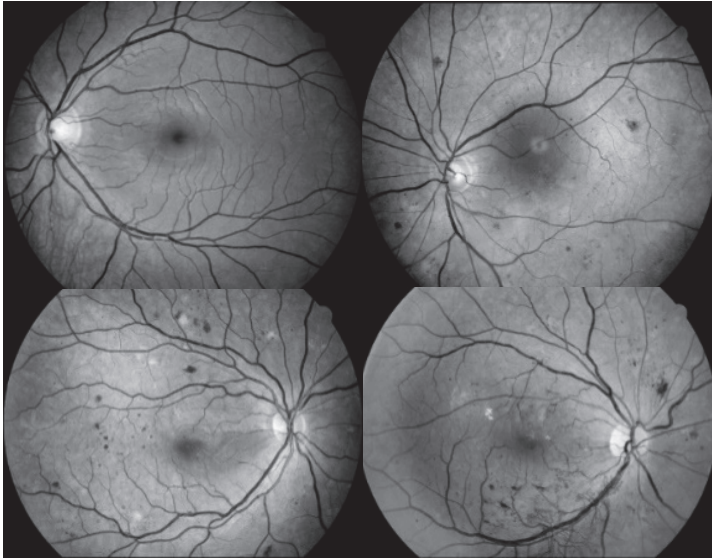


Fig. 3. Top left: Normal fundus, top right: Non-proliferative diabetic retinopathy, bottom left: Pre-proliferative diabetic retinopathy, bottom right: Proliferative diabetic retinopathy. Images from Jukka Veijola and Sylvi Savolainen, Oulu University Hospital.

Non-proliferative diabetic retinopathy

Non-proliferative DR is the least severe and usually symptomless form of DR in the international clinical classification system (Wilkinson *et al.* 2003). A regular ophthalmic follow-up is usually sufficient for patients with non-proliferative DR. It commonly first presents with microaneurysms appearing as small red spots on the superficial layers of the retina (Shah 2008). Microaneurysms are focal saccular dilatations often on the venous side of the retinal capillaries; they usually result from weakening of the capillary walls induced by the loss of pericytes (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007).

Other non-proliferative DR findings include intraretinal haemorrhages, resulting largely from ruptured retinal microaneurysms (Shah 2008). Superficially situated microaneurysms give rise to flame shaped haemorrhages due to the distinctive structure of the surrounding nerve fibre layer. Microaneurysms located deeper in the retina, e.g. in the outer plexiform layer, form haemorrhages with

darker and rounder blot/dot-shapes (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007).

Retinal microinfarctions, also known as cotton-wool spots or soft exudates, originate from occlusions of the precapillary arterioles in the nerve fibre layer (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). The lesions are white and fluffy in appearance and are often situated near to the vascular arcades. The microinfarction's typical appearance is created by the focal accumulation of axoplasmic debris from retinal ganglion cell axons.

Lipid deposits, also referred to as hard exudates, are often associated with retinal oedema. The condition is caused by focal or diffuse vascular hyperpermeability accumulating lipids and proteins in the inner and outer plexiform layers of the retina (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). Aggregated lipoprotein formations can be seen as well-defined yellowish deposits on the fundus. Lipid deposits can vary from singular small specks to diffuse circinate lesions on the edges of oedematous retinal area.

IRMA are dilated irregular capillaries often situated on the edges of perfused and non-perfused areas of the retina (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). They function as collateral vessels, bypassing the obliterated capillary bed. IRMA is a significant indicator predicting the progression of DR (ETDRS research group 1991b).

Venous beading refers to irregular diameter changes, described as a string of sausages, along the length of affected retinal veins (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). The beaded configuration results from segmental dilatations and thinning of the venous walls. Loops or reduplication of venous segments may also appear (Bek 1999). Venopathy can be seen usually near large areas of non-perfused retina. Venous beading is an important indicator of retinal ischemia and according to the Early Treatment Diabetic Retinopathy Study (ETDRS), it is the strongest predictor of progression to PDR (ETDRS research group 1991b).

Pre-proliferative diabetic retinopathy

Pre-proliferative DR is characterised as severe non-proliferative DR. The microvascular fundus changes are more pronounced than in non-proliferative DR but neovascularisation is not present. According to the proposed international

clinical classification of DR, any of the following three characteristics, known as the 4-2-1 rule, are indicative of pre-proliferative DR (Wilkinson *et al.* 2003):

1. Over 20 intraretinal haemorrhages in all four quadrants of the fundus.
2. Definite venopathy in two quadrants.
3. Prominent IRMA in one quadrant.

Potential symptoms of pre-proliferative DR depend mainly on the extent of macular involvement. Pre-proliferative DR may rapidly advance to PDR or remain static. ETDRS, utilizing a more detailed classification of DR, detected severe non-proliferative DR and very severe non-proliferative DR to carry 15% and 45% respective risk of progressing into PDR with high-risk characteristics within one year (ETDRS research group 1991a). Retinal laser photocoagulation may be needed to prevent progression into PDR in advanced cases of pre-proliferative DR.

Proliferative diabetic retinopathy

PDR is an advanced form of DR resulting from the accumulation of microvascular damage in the retina. When the metabolic needs of retinal cells are no longer fulfilled, new vascular growth is induced in an attempt to restore the lost balance. The hallmark of PDR is ischemia-induced neovascularisation of the optic disc and/or retina (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). Neovascularisation often appears near to the vascular arcades on the border of perfused and ischemic retina. In the absence of significant diabetic maculopathy, the first symptom of diabetic ophthalmic pathology noticed by the patient may be blurring of the visual field due to vitreous haemorrhage.

Fragile new blood vessels originate from the venous vasculature and may perforate the inner limiting membrane, gaining access to vitreous. The progression of neovascularisation is usually accompanied by surrounding fibrous connective tissue growth (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). Adhesions are often formed between connective tissue, hyaloid face and retina. The delicate new vessels have a tendency to bleed easily due to contractive forces within the fibrotic tissue, resulting in vitreous or preretinal haemorrhage (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). Vitreous haemorrhage can be inconspicuous or profound, rapidly diminishing visual acuity (VA). Dense intravitreal haemorrhage

often prevents visualization of retina and administration of laser treatment until spontaneous resorption or vitreoretinal surgery. Strong vitreoretinal adhesions may also pull the neurosensory retina from the underlying retinal pigment epithelium resulting in tractional retinal detachment (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007).

Diabetic maculopathy

Diabetic maculopathy is caused by microvascular changes accumulating in the central retina and resulting in ischemic, focal, diffuse or mixed macular oedema (Diabetic retinopathy: Current care guideline 2014, Kanski Jack & Brad 2007). Ischemic macular oedema can be seen in severely non-perfused fundus with leakage of fluid from the remaining vascular structures. Focal macular oedema is predominantly caused by microaneurysms with high permeability. Diffuse macular oedema results from damaged capillary areas leaking fluid between the retinal layers.

Cystoid macular oedema can be seen in conjunction with any of the macular oedema types (Diabetic retinopathy: Current care guideline 2014). It creates a flower petal-pattern in the fovea as vascular leakage forms large fluid filled cystoid spaces in the outer plexiform and inner nuclear layers of the retina. Lipid deposits, consisting of accumulated lipoproteins, may become aggregated in the proximity of any type of diabetic macular oedema.

Optical coherence tomography (OCT) has become an important tool in diagnosing diabetic maculopathy and following the treatment efficacy of macular oedema (Virgili *et al.* 2015). OCT imaging allows a quick and non-invasive evaluation of macular morphology, although FA can still provide more comprehensive information about the retinal vascular status, including the presence of ischemic areas and the extent of the avascular zone (Salz & Witkin 2015).

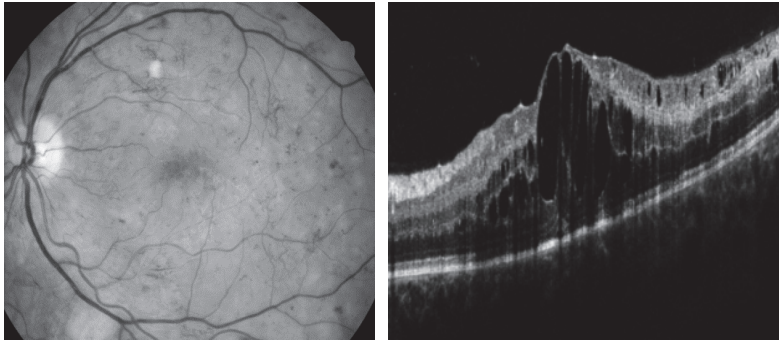


Fig. 4. Fundus photograph and OCT image of a patient with diabetic maculopathy. Images from Jukka Veijola, Oulu University Hospital.

The macular area is responsible for high acuity vision and therefore even minor structural alterations can cause a significant visual impairment (AAO 2015). Diabetic maculopathy is frequently symptomless as long as the central macula remains spared. In advanced cases, macular oedema often involves the fovea and may cause a reduction in VA and metamorphopsia. VA is not dependent only on retinal morphology and accordingly macular thickness may improve significantly in response to treatment while VA remains unrestored or vice versa (Diabetic Retinopathy Clinical Research Network *et al.* 2007). Although T1D related diabetic maculopathy may present at any stage of DR, it is most often seen in conjunction with severe DR (Klein *et al.* 1989). The prevalence of diabetic maculopathy is approximately 10–20% after 15–20 years of T1D duration (Diabetic retinopathy: Current care guideline 2014). Diabetic maculopathy is the second most common cause of T1D related visual impairment after PDR (Jeppesen & Bek 2004, Klein *et al.* 2010).

2.2.4 Risk factors of diabetic retinopathy

The prevalence of DR becomes nearly universal after a long duration of T1D (LeCaire *et al.* 2013). Nevertheless, DR is a heterogeneous microvascular complication in terms of severity and time of presentation. Several non-modifiable (e.g. duration of T1D, pregnancy, puberty, genetic predisposition) and modifiable (e.g. hyperglycaemia, hypertension, dyslipidaemia, nephropathy, anaemia etc.) risk factors influence the development and progression of DR. The modifiable risk determinants require special attention as their contribution to DR

can be influenced positively as well as negatively by self-management and treatment adherence (Keel *et al.* 2014).

Non-modifiable risk factors of diabetic retinopathy

The duration of T1D is a highly predictive non-modifiable risk factor for the onset and progression of DR (Klein *et al.* 1992, Yau *et al.* 2012). The probability of DR increases with cumulating post-diagnosis years. As DR advances, further progression also becomes more probable (Grauslund *et al.* 2009b, Klein *et al.* 2010). However, some patients seem to be non-susceptible to developing diabetic complications, regardless of T1D duration (Sun *et al.* 2011). The factors providing prolonged protection from complications are insufficiently understood.

Puberty is an independent risk factor for DR (Klein *et al.* 1990b). In addition, the number of prepubertal years after T1D diagnosis and their glycaemic quality contribute to the risk of DR (Donaghue *et al.* 2003, Holl *et al.* 1998, Olsen *et al.* 2004). However, the years after puberty have a stronger impact on the development of DR (Olsen *et al.* 2004). The Finnish Diabetic Nephropathy (FinnDiane) Study found that the age at onset of T1D modified the risk of PDR, with subjects diagnosed after 15 years of age displaying a lower risk (Hietala 2013).

Pregnancy temporarily increases the risk of aggravating preconception DR status (DCCT Research Group 2000, Klein *et al.* 1990a). Microvascular fundus changes can progress rapidly during pregnancy due to gestational changes or the related glycaemic fluctuations. The evaluation of DR is advisable before, or at the latest early, in pregnancy (Diabetes: Current care guideline 2013, Diabetic retinopathy: Current care guideline 2014). Advancing DR in need of treatment should preferably be stabilised during preconception care.

There is convincing evidence from family aggregation and twin studies to support the influence of genetic factors on the development and progression of DR (Cho & Sobrin 2014, Kuo *et al.* 2014). The presence of a multifactorial familial component in the development of PDR has also been suggested by the FinnDiane Study (Hietala 2013). Ethnic differences in the prevalence further confirm the importance of genetics in the pathophysiology of DR (Emanuele *et al.* 2005, Yau *et al.* 2012).

Modifiable risk factors of diabetic retinopathy

Hyperglycaemia has been unquestionably linked to the development and progression of DR (DCCT Research Group 1993, Mohamed *et al.* 2007, Wang *et al.* 1993, Yau *et al.* 2012). With every percentile reduction in HbA1c, the risk of DR is estimated to diminish by 30–40% (White *et al.* 2008). However, a substantial reduction as well as an elevation in glycaemic balance may cause reactive exacerbation of DR. The DCCT found early worsening of DR to be associated to the magnitude, but not to the rapidity, of HbA1c reduction during the first six months of intensive treatment (DCCT Research Group 1998). HbA1c variability has been shown to be an independent risk factor for DR (Hermann *et al.* 2014). In the FinnDiane Study, wide HbA1c variability increased the risk of severe DR requiring laser treatment (Hietala 2013).

Hypertension exerts a strong influence on DR status (DCCT Research Group 1993, Klein *et al.* 1998, Mohamed *et al.* 2007, Yau *et al.* 2012). In particular, diabetic maculopathy and macular oedema are known to be exacerbated by elevated BP. Severe hypertension per se additionally can cause hypertensive retinopathy, irrespective of other medical conditions. Thus keeping the BP close to target values, as recommended in the therapy guidelines, confers clear ocular benefits. The risk of DR increases by 10% with every 10 mmHg increase in systolic BP (Klein *et al.* 2008).

In comparison to the previous risk factors, the association between dyslipidaemia and DR is less strong among patients with T1D (Chang & Wu 2013, Lim & Wong 2012). Diabetic nephropathy (Kramer & Retnakaran 2013) and anaemia (Conway *et al.* 2009, Qiao *et al.* 1997) are thought to add to the risk of DR. In addition, a high waist-to-hip ratio may have an unfavourable effect on the development and progression of DR (Chaturvedi *et al.* 2001, Porta *et al.* 2001).

Optimal treatment targets for the primary modifiable risk factors (hyperglycaemia, hypertension and dyslipidaemia) vary slightly according to respective national recommendations. As a general rule, the Finnish Current care guideline recommends the following treatment targets for patients with diabetes: HbA1c <53 mmol/mol (<7.0%), BP <140/80 mmHg and LDL-cholesterol <2.5 mmol/l (Diabetes: Current care guideline 2013). The widely utilized recommendations of the American Diabetes Association (ADA) are very similar to those of the Finnish Current care guideline (American Diabetes Association 2014).

Achieving treatment targets for the primary modifiable risk factors can be challenging. A slight improvement was detected in risk factor management during 1997–2004 in a large Swedish study (Eeg-Olofsson *et al.* 2007). Despite the improvement, the results were evaluated as being unsatisfactory among the majority of study subjects. Of the 13 612 individuals evaluated, only 21% were able to achieve the HbA1c goal of <53 mmol/mol (<7.0%). Furthermore, just 7% reached all three respective treatment goals for HbA1c, BP and cholesterol set by ADA (Eeg-Olofsson *et al.* 2007). According to a recent Finnish study, unattained ADA treatment targets were associated with an increased risk of cardiovascular events and mortality among the T1D population (Lithovius *et al.* 2015).

Table 2. Treatment targets for diabetic patients according to the Finnish Current care guideline (Diabetes: Current care guideline 2013).

Measurement	Target	Note
HbA1c (mmol/mol, %)	<53 (<7.0%)	Individualized if needed
Fasting value (mmol/l)	<7	Self-care value
Postprandial value (mmol/l)	<10	Self-care value
LDL-cholesterol (mmol/l)	<2.5	All diabetics
	<1.8 or ≥50% reduction from baseline values	If atherosclerotic disease, microvascular complications or other atherosclerotic risk factors
Blood pressure (mmHg)	<140/80	

2.2.5 Treatment of diabetic retinopathy

Laser treatment

Lasers of multiple wavelengths can be used to treat different ophthalmic conditions. The high prevalence of diabetes and DR has made the laser an especially important tool in managing DR and in preventing visual impairment (Romero-Aroca *et al.* 2014). Laser treatment to retina is administered with short laser pulses of the selected beam size, creating a focal retinal burn in a controlled manner (Diabetic retinopathy: Current care guideline 2014). The radiation energy of the laser pulse is mostly absorbed by the pigment epithelium and underlying choroid. However, it increases also focally the temperature of the retina and the heat effect alters retinal morphology, creating a permanent scar.

Panretinal laser photocoagulation has been the standard of care for decades in treating PDR (Evans *et al.* 2014, Stitt *et al.* 2015). Panretinal photocoagulation is applied with a relatively large spot size and the treatment covers the majority of retinal surface usually leaving only the macular area untouched (Diabetic retinopathy: Current care guideline 2014, Romero-Aroca *et al.* 2014). The retina has high metabolic activity and reducing the area of retinal tissue by panretinal laser treatment reduces oxygen demand and ischemia in the fundus.

Promptly completed panretinal laser photocoagulation is usually successful in arresting and regressing neovascular growth when delivered without delay (Chappelw *et al.* 2012). Laser treatment is essential in preventing tractional retinal detachment, neovascular glaucoma and ultimately severe impairment of visual function. Although panretinal laser treatment is effective in preventing blindness, the procedure is more likely to retain visual function than to restore it (Cheung *et al.* 2010, Kaiser *et al.* 2000). Consequently, the emphasis must be placed on the early detection of advancing DR.

Laser therapy has also been the standard treatment in clinically significant macular oedema and it still remains widely used (Stitt *et al.* 2015). Laser photocoagulation in the macular area is often performed focally to leaking microaneurysms or more diffusely in a grid-like pattern. The ETDRS has defined characteristics of clinically significant and potentially vision-threatening macular oedema (ETDRS research group 1985). Any one of the following three conditions indicate clinically significant macular oedema and point to a need for treatment.

1. Retinal thickening $\leq 500\mu\text{m}$ of the centre of the macula.
2. Lipid deposits $\leq 500\mu\text{m}$ of macular centre with adjacent retinal thickening.
3. Retinal thickening of at least one disc diameter ($1500\mu\text{m}$) situated at any part within one disc diameter from the centre of the macula.

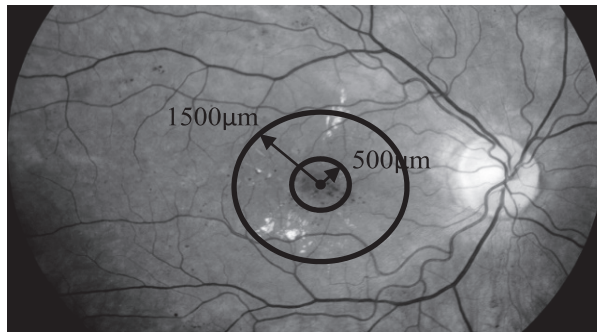


Fig. 5. Clinically significant macular oedema. Original fundus photograph from Jukka Veijola, Oulu University Hospital.

Focal laser treatment has been estimated to reduce the risk of moderate visual loss by 50–70% in treating macular oedema (Mohamed *et al.* 2007). However, there are limitations to the use and efficacy of laser treatment in the macular area (Romero-Aroca *et al.* 2014). Due to the tissue destructive nature of retinal lasers, a corresponding scotoma may be detected in the central visual field after extensive macular laser treatment or inadvertent foveal burn. Laser scars may also expand over time. These characteristics mean that therapeutic laser treatment is applicable only in selective cases of diabetic maculopathy.

Intravitreal treatments

Intravitreal administration of anti-VEGF agents (bevacizumab, ranibizumab, aflibercept) and corticosteroid injections/implants (dexamethasone, triamcinolone, fluocinolone) can be used to treat several ocular conditions e.g. diabetic macular oedema (Antonetti *et al.* 2012, Diabetic Retinopathy Clinical Research Network 2015, Ford *et al.* 2013, Stitt *et al.* 2015). Intravitreal pharmacotherapies have a limited duration of therapeutic effect and periodic injections are often needed. Intravitreal therapy is a non-destructive treatment method compared to laser photocoagulation and its use is not limited by the central location of vascular pathology. However, the need to penetrate through the bulbus in order to access the vitreous cavity carries the risk of endophthalmitis and other rare complications related to intravitreal injections (Shikari *et al.* 2014). Patients with diabetes do not appear to be at increased risk of adverse injection events despite frequent systemic comorbidities and their susceptibility to infections, theoretically predisposing to complications (Shikari *et al.* 2014).

During the last decade, anti-VEGF agents have been proven to be as effective as or even more efficacious than laser therapy in treating diabetic macular oedema (Ollendorf *et al.* 2013, Regnier *et al.* 2014, Virgili *et al.* 2014). Even vision related QoL has been reported to be more favourable in patients treated with intravitreal anti-VEGF injections rather than focal/grid laser treatment (Turkoglu *et al.* 2015).

Corticosteroids are used in treating diabetic macular oedema because of their anti-inflammatory effect. However, intravitreal corticosteroid administration accelerates cataract formation in phakic patients and can increase intraocular pressure (IOP) in steroid responders (Diabetic Retinopathy Clinical Research Network *et al.* 2009, Ford *et al.* 2013). The IOP elevation may be mild and transient or result in secondary glaucoma and require medical or surgical attention.

2.2.6 Complications related to diabetic retinopathy

The likelihood of developing PDR increases with advancing DR. Promptly completed panretinal laser photocoagulation remains the gold standard for the treatment of PDR. Rarely fundus neovascularisation can regress without interventions (Bandello *et al.* 1996). Vitreous and/or preretinal haemorrhage usually occurs if neovascularisation is not managed promptly or efficiently enough. After mild intravitreal haemorrhage, it is often adequate to administer laser treatment in areas of sufficient visibility. Vitreoretinal surgery can be considered in cases of more severe vitreous haemorrhage or anti-VEGF injections, if there is no risk of tractional retinal detachment (AAO 2015, Scanlon 2010).

Poorly managed PDR potentially advances to tractional retinal detachment or neovascular glaucoma (AAO 2015, Sayin *et al.* 2015). Tractional retinal detachment related to PDR is often progressive and requires vitreoretinal surgery in order to maintain visual function (Scanlon 2010, Vote *et al.* 2004). Neovascular glaucoma develops when fibrovascular growth obstructs the anterior chamber angle causing an elevation in IOP (Sayin *et al.* 2015). An acutely painful red eye often forces a patient to seek medical help when secondary angle closure reaches critical limits resulting in a rapid rise in IOP. Topical and oral IOP lowering medications may suffice for the treatment of stabilised neovascular glaucoma in mild cases. Often antihypertensive medication is not adequate and glaucoma surgery is mandatory in order to achieve a satisfactory long-term control of IOP.

PDR is likely to lead to blindness within five to ten years if left untreated (Caird *et al.* 1968, Deckert *et al.* 1967). Debilitating visual loss can be avoided at several stages of the disease with appropriate interventions. However, advanced PDR may still result in severe loss of vision despite best treatment efforts, if the condition is not detected in time or treatment is otherwise delayed.

2.2.7 Visual impairment due to diabetic retinopathy

The International Classification of Diseases (ICD) uses a categorization of visual impairment severity recommended by the World Health Organization (WHO) (WHO 2010). The classification is widely accepted and consists of five categories. In the current ICD-10 revision, the first two categories consist of moderate visual impairment defined as VA of $<0.3 - \geq 0.1$ Snellen and severe visual impairment with VA of $<0.1 - \geq 0.05$ Snellen. Blindness is divided into three categories ranging from <0.05 Snellen to no light perception (WHO 2010). ICD-10 instructs VA to be measured with presenting refractive correction if any.

DR is one of the leading causes of blindness among the working aged population in the industrialized countries (Congdon *et al.* 2003). In 2013, 9% of visual impairment among 18–64 year-olds in Finland was attributable to DR and it was the fourth most common reason after hereditary retinal dystrophies (21%), disorders of visual pathway (19%) and congenital disorders (12%) (Ojamo 2014). DR was also the second most frequent cause of new-onset visual impairment (17%) among the Finnish working aged population (Ojamo 2014).

Visual impairment related to T1D is commonly caused by PDR and less frequently by diabetic maculopathy. The total number of registered visually impaired persons in Finland was 18 388 in 2013, 606 (3.3%) of them had been impaired specifically due to PDR while 270 (1.5%) were classified as non-PDR (Ojamo 2014). With respect to the WTDRS subjects exhibiting any visual impairment, 75% had developed PDR and 17 % had clinically significant macular oedema (Klein *et al.* 2010). In Denmark during the period 1993–2002, PDR was the primary reason for registered blindness among the T1D population, accounting for 66% of all occurrences, while only 4% of cases were caused by diabetic maculopathy (Jeppesen & Bek 2004).

Diabetic fundus pathology is not the only cause of visual loss in the T1D population. Readily curable ocular conditions, like diabetic cataract, may lead to long-term visual impairment in those countries with inadequate resources or limited access to healthcare (Khanna *et al.* 2011, Pascolini & Mariotti 2012).

However, T1D poses also several other unresolved challenges in the developing countries. More pressingly than any ophthalmic impairments, from a global perspective, a lack of access to insulin is still the most common cause of a death in a child with diabetes (Gale 2006).

Reduction in VA can have a detrimental effect on a patient's HRQoL, future prospects and life expectancy. Even in the industrialised countries, the mortality of T1D population is significantly higher in those individuals who have become blind (Grauslund *et al.* 2009a). The unfavourable prognosis may be partly explained by the repercussions of blindness itself as well as the probable overall advanced state of other diabetic complications.

Not all patients with T1D will suffer significant visual loss but the incidence has remained alarmingly high. In particular, patients lost from a DR screening programme are at risk of visual impairment (Echouffo-Tcheugui *et al.* 2013). Promisingly, improved DR screening modalities and efficient care in the Northern Ostrobothnia Hospital District reduced visual impairment due to DR by 86% compared to the concurrent reduction of 35% in the rest of Finland (Hautala *et al.* 2014a). As described in the previous chapter, PDR usually leads to blindness if no treatment is administered. Panretinal photocoagulation can reduce the risk of moderate to severe visual loss by 50% in patients with pre-proliferative DR or PDR (Mohamed *et al.* 2007). Although modern healthcare can prevent most cases of debilitating DR, a clear increase is detected in the incidence of blindness due to PDR after a 20 years' duration of T1D (Jeppesen & Bek 2004).

The WESDR reported the 25-year incidence of any visual impairment (VA ≤ 0.5 Snellen in better eye) among patients with T1D to be 13%. With respect to severe visual impairment (VA ≤ 0.1 Snellen), the incidence was 3%. The strongest predictors of visual impairment were hyperglycaemia, severity of DR, smoking and cataract (Klein *et al.* 2010). In a Danish population-based cohort of patients with T1D, the cumulative crude incidence of blindness was 8% after a 25-year follow-up (Grauslund *et al.* 2009a). The presence of diabetic maculopathy and poor glycaemic control were identified as risk factors for blindness.

A decrease in prevalence of visual impairment has been detected in the more recent WESDR cohorts presumably due to improvements in T1D and DR treatments and outcomes (Klein *et al.* 2009). Similarly, the incidence of vision-threatening DR after 20 years' duration of T1D declined from 43% to 18% when the WESDR cohort was compared to a similar population-based WDRS cohort diagnosed on average two decades later (LeCaire *et al.* 2013). These results are in concordance with the WESDR and WDRS studies also reporting a decreased

incidence of severe DR and PDR among more recent T1D cohorts (Klein *et al.* 2008, LeCaire *et al.* 2013).

2.2.8 Screening of diabetic retinopathy in Finland

DR screenings are arranged in the Finnish municipalities according to the recommendation of the Finnish Current care guideline (Diabetic retinopathy: Current care guideline 2014). Municipal healthcare centres have a responsibility to provide DR screening without charge for patients with diabetes living in their catchment districts. Finnish nationwide recommendations for screening practises of DR have been implemented since 1992.

Digital imaging with sufficient resolution and the use of mydriatic eye drops are advocated for retinal screening purposes. Digital fundus images achieve approximately equal sensitivity in the detection of DR as the standard colour photography and they display better sensitivity than mydriatic ophthalmoscopy (Gangaputra *et al.* 2011, Lin *et al.* 1999, Lin *et al.* 2002, Williams *et al.* 2004). Pharmacologically induced mydriasis does improve the quality of images irrespective if a non-mydriatic or a mydriatic fundus camera is being used (Murgatroyd *et al.* 2004, Pugh *et al.* 1993). Two images of at least 45°, preferably 60°, are recommended for the screening of DR (Diabetic retinopathy: Current care guideline 2014). One image is centred at the fovea and the other at the optic disc. Fundus photographs are often first evaluated by a primary care physician or a specially trained nurse and if needed, the images are forwarded to an ophthalmologist for consultation.

T1D requires lifelong ophthalmic monitoring. The national recommendations enable good screening coverage and appropriately timed referral to treatment. Regular DR screening in Finland occurs from the age of ten years or from the time of diagnosis in older patients (Diabetic retinopathy: Current care guideline 2014). The screening is continued every other year until any sign of DR appears. Thereafter fundus photographs are taken every year or more often if needed. The screening interval can be adjusted to meet individual needs e.g. in cases of unsatisfactory glycaemic balance. The patient is referred to an ophthalmologist if fundus images indicate a need for a more thorough examination or treatment. During pregnancy, DR screening should be arranged according to the severity of DR, nephropathy and BP (Diabetic retinopathy: Current care guideline 2014). Gestational diabetes does not require fundus assessment.

DR screening has proved to be highly cost effective (Javitt & Aiello 1996, Jones & Edwards 2010, Li *et al.* 2010b, Pajunpää 1999). Systematic screenings also appear to reduce the prevalence of visual impairment among T1D patients (Agardh *et al.* 1993, Kristinsson *et al.* 1997). In 1992, Arhus County in Denmark implemented a DR screening program and during the following decade, the frequency of PDR induced blindness was observed to decline among the T1D population (Jeppesen & Bek 2004). In Northern Finland, during 2007–2012 effective screening of DR by mobile eye examination unit in combination with timely referral and care has reduced visual impairment due to T1D and type 2 diabetes (T2D) by almost 90% (Hautala *et al.* 2014a). Telemedicine applications and mobile units have proved efficient and cost-saving in DR screening. This form of screening is currently especially applicable in remote and sparsely populated areas but in the future, telemedicine technology is likely to become more broadly exploited in diabetes management (Balkhi *et al.* 2015, Bashshur *et al.* 2015).

2.2.9 Other visual and ocular morbidities of type 1 diabetes

T1D manifests itself throughout the body in numerous ways. The microvascular alterations of DR are especially easy to detect due to the transparency of retina. However, several other parts of the eye and the visual pathway can be affected, potentially causing disturbances in vision and other functions of the eye (Kaarniranta & Sorri 2008). Follow-up and treatment may be needed depending on the resulting impairment.

Some morbidities are easily detectable during a basic ophthalmic examination such as the development of diabetic cataract. However, several subclinical dysfunctions on the visual pathway require more refined methods of testing. Abnormal responses from subjective psychophysical and objective electrophysiological tests are often detectable before any overt pathology is present in retina (Ewing *et al.* 1998, Parisi & Uccioli 2001). This indicates that the causes of visual dysfunction related to T1D are not all of vascular origin but also neurodegenerative alterations are involved (Barber 2003, Layton *et al.* 2006). Some psychophysical and electrophysiological tests have been considered potentially useful in predicting the development and progression of DR (Ewing *et al.* 1998).

Diabetic cataract

Intraocular lens opacification i.e. cataract formation, is accelerated by T1D. A diabetic cataract can present in the acute (“true”) juvenile form, developing within days to weeks (Bron *et al.* 1993). The more common type is the slowly developing adult form causing VA reduction appearing years or decades after the diagnosis of T1D. The polyol pathway is thought to be of significance, especially in the development of the rapidly forming diabetic cataract (Chung *et al.* 2003, Pollreis & Schmidt-Erfurth 2010). The process is characterised by increased aldose reductase activity leading to an accumulation of sorbitol in the lens. This creates increased osmotic stress with swelling and breakdown of the lens fibres, resulting in cataract formation.

Juvenile diabetic cataract typically presents with bilateral cortical snowflake like specks and posterior subcapsular opacities (Falck & Laatikainen 1998). The development of cataract has been associated with prolonged symptoms of T1D before diagnosis as well as DKA or high HbA1c at diagnosis (Datta *et al.* 1997, Falck & Laatikainen 1998). Juvenile diabetic cataract can sometimes be the first detected sign of T1D in a paediatric patient (Taskapili *et al.* 2008, Uspal & Schapiro 2011). On rare occasions, a rapidly formed lens opacification can spontaneously resolve after glycaemic balance has been restored close to the normal range (Jin *et al.* 2012).

The slowly developing diabetic cataract in adults is more frequently detected than the juvenile type. Morphologically the adult form is quite similar to the senile cataract encountered in the non-diabetic population, although it often develops earlier and progresses more rapidly (Bron *et al.* 1993). Diabetic cataract formation in adults has been linked to several factors e.g. increasing age, duration of T1D, poor glycaemic control and DR (Janghorbani *et al.* 2000, Klein *et al.* 1985). In most cases, the restoration of VA requires cataract surgery among both paediatric and adult patients (Obrosova *et al.* 2010, Wilson *et al.* 2007). According to a Danish study, adult patients with T1D require cataract surgery on average 20 years earlier than their non-diabetic counterparts (Grauslund 2011).

Refractive change

Phakic patients with T1D often notice blurring of vision when experiencing rapid glycaemic fluctuations. This type of visual disturbance is predominantly caused by a refractive change within the eye. The effect can be transient or long-term

depending on the underlying glycaemic status. According to studies, the refractive power of an eye can shift in the myopic as well as hyperopic direction due to glycaemic changes (Fledelius *et al.* 1990, Giusti 2003, Sonmez *et al.* 2005).

After initiating treatment for hyperglycaemia, phakic patients with declining plasma glucose levels frequently experience a transient hyperopic shift (Giusti 2003, Lin *et al.* 2009, Saito *et al.* 1993). The hyperopic refractive change is believed to result mainly from osmotic lenticular swelling leading to a decrease in the index of refraction (Giusti 2003, Lin *et al.* 2009). Although the total refractive power of an eye depends on an array of ocular biometrics, factors other than the refractive index of the lens do not seem to contribute significantly to this change (Giusti 2003, Li *et al.* 2010a). The refractive power usually returns close to baseline within a few weeks or months (Giusti 2003, Li *et al.* 2010a).

Electrophysiological changes

Electroretinogram. Individuals with T1D may develop various signs of subclinical retinal dysfunction prior to manifesting DR. The electroretinogram (ERG) is a diagnostic tool providing an objective assessment of the function of retina by measuring the electrical response to a light stimulus. ERG can identify subtle biochemical and functional deficits at the retinal level in the early stages of the disease (Ewing *et al.* 1998).

Changes in ERG are frequently detected among patients with T1D. PDR and administered retinal laser treatment are thought to accentuate these abnormalities (Ewing *et al.* 1998). Degraded neuroretinal function, evaluated by multifocal ERG, has been associated with poor glycaemic balance in adolescents without overt DR (Laron *et al.* 2012).

Visual evoked potential. The visual evoked potential (VEP) assesses the function of the visual pathway from the retina to the visual cortex. VEP detects possible conduction deficits and measures the electrical potential generated by the occipital cortex in response to a visual stimulus. VEP is efficient at identifying alterations primarily in the anterior visual pathway.

Several studies have found significant abnormalities in VEP latencies and amplitudes among diabetic populations without overt DR (Ewing *et al.* 1998). Progressive increases in VEP latency values are indicative of damage of the retinal ganglion cells (Karlica *et al.* 2010). However, improving glycaemic balance in patients with T1D and no DR has been shown to improve significantly also VEP parameters (Matanovic *et al.* 2012).

Psychophysical changes

Contrast sensitivity. Contrast sensitivity measures the ability of the visual system to distinguish between different intensities of light and dark i.e. differentiating a visual object from its background. Decreased contrast sensitivity can be an early sign of accumulating visual pathway dysfunction caused by T1D. Abnormal contrast sensitivity does not necessarily interfere with VA testing because the tests are performed with high contrast optotypes (Hashemi *et al.* 2012). Patients with reduced contrast sensitivity can experience disturbing haziness in vision despite unaffected results on VA testing.

A reduction in contrast sensitivity is a common finding in patients with T1D (Banford *et al.* 1994, Di Leo *et al.* 1992). The contrast sensitivity of diabetic adolescents without DR was evaluated with the CSV-1000 device and significant reductions were detected at all tested spatial frequencies (Georgakopoulos *et al.* 2011). Both dynamic and static test modes were able to detect contrast sensitivity abnormalities before any overt DR had developed (Di Leo *et al.* 1992).

Colour vision. An acquired colour vision defect, predominantly on the yellow-blue axis i.e. tritanopia, is a frequent finding in the T1D population (Bresnick *et al.* 1985, Fong *et al.* 1999). Tritanopia very rarely has a congenital origin unlike defects in the red-green axis. Some have argued that T1D reduces all colour discrimination equally, but that tritanopia is more easily detected mainly because of the yellowing of the lens highlighting the effect (Tregear *et al.* 1997). Acquired dyschromatopsia may complicate the use of any colour-coded self-care equipment e.g. blood or urine test strips (Lombraile *et al.* 1984, Mantyjarvi 1992).

The severity of the detected colour vision defect often correlates with the degree of diabetic fundus changes, especially those involving the macular area (Bresnick *et al.* 1985, Fong *et al.* 1999, Tregear *et al.* 1997). However, defects in colour vision have been observed also in diabetic adolescents with good VA, no clinical signs of DR and normal retinal angiography (Giusti 2001, Hardy *et al.* 1992). A study assessing the colour vision of 102 patients with T1D applying the Farnsworth-Munsell 100-Hue test detected dyschromatopsia on a yellow-blue axis in 70% of the patients even though they had normal VA and no signs of DR (Muntoni *et al.* 1982).

Dark adaptation. The human eye can function under a wide range of luminance levels due to adaptive processes in the retina. The recovery time of bleached out rods to regain reasonable sensitivity in the dark takes tens of minutes following retinal exposure to intense illumination (Lamb & Pugh 2004). The

sensitivity of retina can increase up to an hour in dim illumination with ongoing regeneration of rod photopigments called rhodopsin. The time of recovery, also known as dark adaptation, can be significantly prolonged or the photochemical regeneration altogether restricted due to the impaired retinal function associated with DR. Dark adaptation is often compromised in patients with diabetes, even in those with non-proliferative fundus changes and unaffected VA (Jackson *et al.* 2012).

2.3 Influence of type 1 diabetes on quality of life

Maintaining overall well-being and QoL is an important element in the management of T1D and any other chronic disease. QoL is a dynamic entity influenced by the individual's expectations and present circumstances. These features may enable adaptation and recovery of acceptable QoL even in underprivileged situations. The WHO defines QoL as an individual's perception of their position in life in the context of the culture and the value system in which they live and in relation to their goals, expectation, standards and concerns (WHO 1995). Current therapy guidelines increasingly often include the aim of preserving or improving patient's HRQoL.

T1D poses a unique challenge to the QoL of the affected patients. The disease mandates permanent changes in lifestyle from the day of diagnosis. Constant mindfulness for dietary intake, blood glucose stability and insulin regulation can upset an individual's daily routines (Duru *et al.* 2015, Reddy *et al.* 2015). The complex treatment regimen becomes more familiar as time elapses from onset. However, with time also diabetic complications, comorbidities and possibly a fear of future ramifications may appear and add to the physical and psychological burden of T1D. Nowadays patients live with chronic conditions like T1D for numerous decades and therefore progressively more emphasis is being placed on restoring, maintaining and improving their HRQoL.

2.3.1 Management of type 1 diabetes

The management of T1D is indisputably challenging at any given age and the diagnosis impacts comprehensively on the lives of affected individuals. During the past few decades, T1D management has become intensified and increasingly detailed with the developments made regarding medications, glucose monitoring, therapy guidelines and patient education (Giani *et al.* 2015). The involvement of

multidisciplinary diabetes teams is widely recommended and beneficial in achieving good short and long-term results, possibly reducing also the incidence and severity of T1D related complications (Codispoti *et al.* 2004, Diabetes: Current care guideline 2013, Likitmaskul *et al.* 2002).

T1D self-care can be demanding even with access to high quality care and continuous patient education. Executive functions are important in independent and successful diabetes management (McNally *et al.* 2010). Estimating the influence of a skipped meal, strenuous exercise or an acute illness on the insulin demand requires both awareness of the pathology of T1D and problem solving skills. Mild neurodevelopmental deficits are commonly associated with T1D and they may per se influence the capacity of some individuals to manage T1D satisfactorily (Nylander *et al.* 2013). Currently only a minority of patients with T1D achieve all of the recommended treatment goals (Eeg-Olofsson *et al.* 2007, Lithovius *et al.* 2015).

Treatment adherence problems are prevalent in all age groups but especially during teenage years (Borus & Laffel 2010). Adolescence is a psychologically vulnerable transitional period to autonomy and adulthood, and this already fraught process can be easily further complicated by a chronic illness. Adolescents rarely possess the emotional maturity needed to adhere incessantly to the routines and punctuality that T1D demands. Psychosocial issues and the overall strain of coping with a chronic disease may become manifest in missed clinical appointments and poor self-care.

Less than one in every five of a cohort of Finnish adolescents with T1D reported complying fully with their health regimens (Kyngas 2000). Home monitoring proved especially challenging as 51% showed poor compliance with home monitoring instructions (Kyngas 2000). Similarly, a recent study estimated that 59% of a population with T1D were non-adherent to dietary advice, 42% were non-adherent to physical activity recommendations and 88% were non-adherent to their prescribed insulin regimen (Riaz *et al.* 2014).

According to the Hvidoere reports, patients' metabolic control in several paediatric diabetes clinics worldwide was suboptimal in the mid-1990s with mean HbA1c of 71mmol/mol (8.6%) and no significant improvement was achieved in glycaemic balance during the following decade (de Beaufort *et al.* 2007, Mortensen & Hougaard 1997). However, numerous fairly recent accounts have described improved glycaemic outcomes in populations with T1D (Bulsara *et al.* 2004, Margeirsdottir *et al.* 2010, Svensson *et al.* 2009). In Slovenia, a nationwide prospective study of paediatric patients with T1D found that median HbA1c

levels had declined from 78 mmol/mol (9.3%) in 2000 to 61 mmol/mol (7.7%) in 2011 due to a new treatment modality (Dovc *et al.* 2014). A prospective multicentre study observed a decrease in hypoglycaemic events despite a simultaneous significant reduction in HbA1c levels during the past decade in Germany and Austria (Rosenbauer *et al.* 2012).

The frequently reported unsatisfactory results in T1D care indicate that the current knowledge and treatment modalities are not being optimally utilized. A lack of treatment adherence as well as other self-care problems quickly manifest themselves e.g. in elevations in the HbA1c values (Hood *et al.* 2009). Only 35% of children and adolescents achieved the target HbA1c of <53 mmol/mol (<7.0%) in a large Swedish study involving 20 paediatric clinics (Hanberger *et al.* 2008). If the self-management of T1D is neglected often, this may irreversibly accelerate the development of diabetic complications. However, an elevated HbA1c value does not necessarily infer poor treatment adherence as inadvertent factors, e.g. incorrect injection technique, can keep the blood glucose concentration at a suboptimal level (Toljamo & Hentinen 2001).

Significant glycaemic fluctuations are not uncommon, although much self-care time is spent in attempting to balance blood glucose levels (Reddy *et al.* 2015). Patients with T1D may develop a fear of hypoglycaemic episodes due to the negative consequences and unpleasant symptoms related to severe hypoglycaemia (Anderbro *et al.* 2010, Wild *et al.* 2007). The fear commonly correlates to the frequency of previously experienced severe hypoglycaemic events and it is more prevalent in females with T1D than in males. (Anderbro *et al.* 2010). Avoiding hypoglycaemia often leads to maintaining blood glucose level at an unnecessarily high value in order to minimize the risk of a hypoglycaemic episode. This practice comes potentially at a high future cost since frequent hyperglycaemia will have an unfavourable impact on subsequent health outcomes (Wild *et al.* 2007).

Many diabetic patients feel uneasy performing self-care tasks in public (Davies *et al.* 2013, Peyrot *et al.* 2012). Consequently, insulin administration or glucose monitoring may be preferably skipped or delayed in these situations. Other commonly reported reasons, in addition to public embarrassment, for insulin non-adherence among a population with T1D and T2D were travelling, skipped meals, stress/emotional problems and being too busy (Peyrot *et al.* 2012). In an era when self-monitoring gadgets for various purposes are exceedingly popular, glucose monitoring and insulin administration are still often kept private and possibly considered as stigmatising. Self-consciousness about T1D and its

management remains a significant source of diabetes related distress (Balfe *et al.* 2013). Treatment satisfaction has reportedly conferred a significant positive impact on self-care adherence among adults (Barbosa *et al.* 2012, Hendrychova *et al.* 2013).

2.3.2 Psychosocial disorders related to type 1 diabetes

Living with a chronic illness necessitates adaptation and therefore behavioural self-regulation is essential for the successful management of T1D (Northam *et al.* 2006). The challenges faced during the course of the disease can be exacerbated by the increased risk of psychiatric disorders associated with T1D (Maia *et al.* 2012, Northam *et al.* 2005). Psychosocial problems related to T1D have significant clinical importance and they are associated with an adverse disease outcome. The International Society for Pediatric and Adolescent Diabetes stated in their Consensus Guideline 2000 that psychosocial factors are the most important influences affecting the care and management of diabetes (ISPAD 2000). The ADA has recommended screening the diabetic population regularly for psychosocial problems e.g. depression, diabetes related distress and eating disorders (ADA 2014).

T1D has been associated with an increased frequency of clinical depression. The reported prevalence of comorbid depression among the T1D population has varied significantly from study to study. Two review articles estimated the prevalence of clinical depression in subjects with T1D to be 12% (Barnard *et al.* 2006, Roy & Lloyd 2012). In comparison, 3% of the non-diabetic controls had clinical depression (Roy & Lloyd 2012). Patients suffering from T1D related complications seem to be especially susceptible to depression (Gendelman *et al.* 2009).

Depression and depressive symptoms have been repeatedly associated with poor glycaemic balance and diminished adherence to self-care routines (Corathers *et al.* 2013, Gonzalez *et al.* 2008, Kongkaew *et al.* 2014, Roy *et al.* 2007). However, a recent study compared adolescents with good and poor glycaemic control and found one in five patients with T1D to have depressive symptoms irrespective of the quality of glycaemic control (Zdunczyk *et al.* 2014). Patients suffering from depressive symptoms have been reported to be at an increased risk for hospitalization for diabetic complications (Stewart *et al.* 2005). In a Finnish T1D population, a need for antidepressants was linked to a higher mortality rate in women (Ahola *et al.* 2012).

Diabetes distress is a distinct diabetes-specific condition consisting of the emotional burden, frustrations and worries directly related to managing this severe chronic condition (Balfe *et al.* 2013, Gonzalez *et al.* 2011). Approximately one third of the T1D population has been estimated to experience significant diabetes related distress (Hislop *et al.* 2008). Similarly to other conditions disrupting self-care routines, diabetes distress has also been reported to generate poorer glycaemic results (Hislop *et al.* 2008). A study examining sources of diabetes distress in young adults with T1D found the common causes to be self-consciousness/stigma, day-to-day diabetes management difficulties, having to struggle with the bureaucracy of the healthcare system, concerns about the future and apprehension about pregnancy (Balfe *et al.* 2013).

Body image dissatisfaction and self-esteem issues are common nowadays, particularly among teenagers and young adults. During adolescence and early adulthood especially females with T1D may regard under-dosing or omitting insulin injections as a way to control body weight (Jones *et al.* 2000, Peveler *et al.* 2005, Polonsky *et al.* 1994, Rydall *et al.* 1997). Insulin omission is the most frequent cause of recurrently occurring DKA (Wolfsdorf *et al.* 2014).

More than one in every four young females with T1D has been estimated to exhibit disordered eating behaviour (Peveler *et al.* 2005, Rydall *et al.* 1997, Wisting *et al.* 2013). Disordered eating is strongly associated with poor metabolic control (Jones *et al.* 2000, Rydall *et al.* 1997, Young *et al.* 2013). Impaired glycaemic balance puts these young patients at risk for the early development of acute and chronic diabetic complications (Jones *et al.* 2000, Peveler *et al.* 2005). In particular, the onset of DR was observed to advance due to the effects of disordered eating behaviour in a study population consisting of young women with T1D (Rydall *et al.* 1997). Disordered eating habits also significantly increased the mortality among T1D population (Peveler *et al.* 2005).

2.3.3 Health related quality of life among patients with type 1 diabetes

Improved treatment modalities have increased the life expectancy of several patient groups and nowadays there is more emphasis placed on restoring, maintaining and improving the HRQoL of the chronically ill. The HRQoL measurements provide an important indicator of health especially in chronic or life threatening conditions (Eiser & Jenney 2007). Accordingly, the HRQoL has become an increasingly utilized health outcome in both clinical work and

research. It is a highly subjective measure assessing the patient's perceived health. HRQoL takes into account the individual's personal and social context, ensuring that the focus of care is on the patient rather than on the disease (Higginson & Carr 2001).

Several disease-specific and generic instruments have been developed for measuring HRQoL. Furthermore, age-appropriate tests are available for children and adolescents. Chronic illnesses can reportedly interfere profoundly with an individual's physical, social and emotional welfare. A decline in HRQoL among the T1D population can result from any of the physical deficits associated with the disease as well as the psychological burden of living with the chronic condition. Some changes in HRQoL can manifest themselves already during childhood (Duru *et al.* 2015).

T1D commonly lowers HRQoL of affected individuals, but not necessarily to the degree of other serious chronic diseases (Rubin & Peyrot 1999). A patient's HRQoL can fluctuate during the course of the disease due to changes in physical and emotional well-being. A young T1D patient with good health may not differ greatly from a non-diabetic youth in terms of general QoL (Laffel *et al.* 2003). However, diabetes distress and the overall burden of managing a chronic disease may impact negatively on a patient's HRQoL even before any significant diabetic complications have developed. Accordingly, children and adolescents with T1D have rated their HRQoL as lower than healthy peers in several studies (Graue *et al.* 2003, Kalyva *et al.* 2011).

Parents have estimated that T1D impacts more on their child's HRQoL than the affected children report themselves (Chaplin *et al.* 2009, Kalyva *et al.* 2011). QoL is a dynamic measure which is self-calibrating to some extent according to the present circumstances. The burden of the disease may seem greater to a non-affected individual than the patient accustomed to the self-care routines. In particular, the early onset of T1D can facilitate good adaptation. Subjects with an onset of T1D under five years of age were evaluated to have better self-reported HRQoL during adulthood compared to peers with a later onset (Trento *et al.* 2014). The favourable result related to earlier onset was thought to be partly due to the better adaptation to the disease in the absence of recollection of the trauma related to the onset or to their life prior to T1D diagnosis. It has been reported that adolescents experience greater difficulty in accepting their diagnosis compared to younger children (Chaplin *et al.* 2009).

The development of T1D related complications and comorbidities further threaten an individual's HRQoL. Psychosocial disorders are particularly common

among the T1D population e.g. depressive symptoms can exert a significant influence on HRQoL even in paediatric patients with good metabolic control (Zdunczyk *et al.* 2014). Chronic fatigue was reported by 40% of T1D population in a recent study as compared to 7% of matched controls (Goedendorp *et al.* 2014). Chronic fatigue has been associated with an excess of functional impairments and patients rated it as the most burdensome T1D related symptom (Goedendorp *et al.* 2014).

DR may induce significant social and emotional strain on the patient and lower HRQoL at various stages of disease severity (Fenwick *et al.* 2012, Sharma *et al.* 2005). Feelings of vulnerability to vision loss are common and can cause diabetes distress even before any reduction in visual functions has occurred. Detection of DR per se may generate anxiety for the future and negatively affect HRQoL due to the emotional reaction to the diagnosis and the treatment that may be required (Sharma *et al.* 2005). Patients with advanced DR are reportedly willing to trade off a significant time of their remaining lifespan (mean time trade-off score = 0.77 -0.8) if that would mean that they did not have to experience any visual dysfunction (Sharma *et al.* 2005).

Two separate studies observed visual loss of either two or three ETDRS lines to reduce not only domains of vision-related HRQoL, but also the domains of mental health, role difficulties, dependency and driving (Hirai *et al.* 2011, Matza *et al.* 2008). Apprehensions about a loss of mobility and independence related to decreasing visual functioning are common among patients with T1D and T2D (Coyne *et al.* 2004). DR induced visual impairment can lead to permanent cancellation of the driver's license for medical reasons and result in transportation difficulties, often increasing an individual's social isolation (Fenwick *et al.* 2012). Inability to drive due to poor vision can also be a cause of unemployment and loss of income (Fenwick *et al.* 2012).

Visual impairment and the lifestyle changes it enforces can cause worsening of family relationships (Fenwick *et al.* 2012). Severe vision loss due to DR has been linked to disruption of family functioning and a higher prevalence of divorce compared to the general population (Bernbaum *et al.* 1993). Living without a partner may lower QoL significantly and have a negative impact on HbA1c levels (Imayama *et al.* 2011, Joensen *et al.* 2013). Advancing age and potential diabetic complications often limit a patient's self-sufficiency and deteriorating health increases the demand for support and healthcare services. Similarly to the situation in non-diabetic subjects, increasing age has been clearly linked to decreasing HRQoL among patients with T1D (Ahola *et al.* 2010, Hirai *et al.*

2011). The decline in HRQoL related to aging can also be detected in the absence of significant diabetic complications (Ahola *et al.* 2010).

2.4 Social status of patients with type 1 diabetes

T1D is associated with a variety of physical and psychological complications and comorbidities. In an advanced form, they may cause major disruption to a patient's life and limit self-sufficiency, threaten economic independence and reduce life expectancy. The increased risk for neurocognitive deficits and an excess of psychosocial challenges can influence the subject's educational achievements and thus also future prospects in the labour market. In susceptible individuals, the negative effect of T1D may lead to fewer career opportunities with lower salaries (Milton *et al.* 2006, Persson *et al.* 2013).

Potential physical and psychological impairments related to T1D may negatively guide decision-making on important issues e.g. concerning education, career development, relationships and family planning. Among a population with T1D and T2D, 74% of patients reported that their illness had influenced one or several major life changing decisions (Bhatti *et al.* 2010). Although the most frequently affected major life changing decision was early retirement, also other decisions were influenced by the disease e.g. change of profession, having children and relationships (Bhatti *et al.* 2010).

The consequences of T1D on an individual's social and socio-economic development are less clearly defined than the well-known medical ramifications of the disease. Considering the impacts that T1D has on multiple facets of a patient's life, this chronic disease may very plausibly also be influencing an individual's overall social performance.

2.4.1 Schooling

Most diabetic children seem to manage their educational obligations without encountering major problems. However, neuropsychological evaluations have revealed mildly adverse neurodevelopmental outcome in patients with T1D (Gaudieri *et al.* 2008, Northam *et al.* 2001). Several studies have also indicated that T1D can evoke a subtle but significant negative effect on the individual's academic skills and performance (Dahlquist *et al.* 2007, Milton *et al.* 2006, Persson *et al.* 2013, Wodrich *et al.* 2011).

School aged children with T1D are more frequently absent from school compared to siblings without T1D or other healthy peers (Milton *et al.* 2006, Wodrich *et al.* 2011). A study assessing diabetic adolescents and their healthy siblings found that children with T1D missed an average of 10 additional days of school compared to the non-diabetic siblings with the mean absentee rate rising close to 10% of scheduled school days (Parent *et al.* 2009). In addition to sickness absences, classes are missed regularly due to attending T1D related clinical appointments. Additional small breaks may be necessary during school days to measure blood sugar, have a snack or recover from high/low blood sugar. These minor disruptions to school work most likely go unrecorded and therefore the actual active school attendance may be poorer than listed in the absence records. Increased absenteeism may in part adversely affect the academic performance of children with T1D.

There are numerous reports for and against the long-term effects of recurrent hypoglycaemic attacks and high hyperglycaemia on cognitive functioning. According to a Finnish study, severe hypoglycaemic episodes during childhood can lead to more pronounced neuropsychological deficits and learning difficulties with an increased need for part-time special education (Hannonen *et al.* 2003). Irrespective of the potential long-term effects, neuroglycopenia during a hypoglycaemic episode induces a transient decline in neurocognitive functioning (Bischoff *et al.* 1992, Graveling *et al.* 2013, Rodrigues Vilela *et al.* 2014, Wright *et al.* 2009). The reduced cognitive state following a hypoglycaemic incident can last for some hours and adversely influence the child's performance and learning during that school day.

T1D related impairment of cognition is especially prominent in those with an early onset of the disease (Biessels *et al.* 2007, Desrocher & Rovet 2004, Gaudieri *et al.* 2008). Children with early onset of T1D are also more likely to suffer from minor learning difficulties during their early school years (Hannonen *et al.* 2010). The increased risk is seen independently of past occurrence of severe hypoglycaemia or DKA (Hannonen *et al.* 2012). In addition, the overall school achievement of children with early onset of T1D is estimated to be less favourable than their peers with a later onset of the disease (Gaudieri *et al.* 2008). This is a worrying trend, as the age at onset is declining and a growing number of children are being diagnosed with T1D.

In Sweden, school performance of adolescents with T1D was evaluated in two respective studies. Final school grades at the level of compulsory education (16 years of age) and upper secondary school (19 years of age) were compared to

those of the general population (Dahlquist *et al.* 2007, Persson *et al.* 2013). Mean final grades achieved in compulsory school and theoretical programs in upper secondary school were lower among the students with T1D. The pupils with early onset of T1D (0–4 and 0–2 years, respectively) attained the least favorable results in both studies (Dahlquist *et al.* 2007, Persson *et al.* 2013).

2.4.2 Worklife

T1D poses some limitations regarding the pursued line of work. Restrictions are in place to prevent any serious consequences of potential glycaemic fluctuations. Some professions are deemed unsuitable for patients with T1D e.g. pilot, police, commercial diver and firefighter (Finnish Diabetes Association 2008). Likewise, it is considered inappropriate to have a job operating heavy machinery, driving public transportation or doing any other occupation posing a risk to oneself or others in case of a sudden incapacity caused by hypoglycaemia. Occupations with restricted self-care possibilities are also less suitable for persons with T1D. It is also worth considering whether the desired profession involves shift work, working alone or at heights.

Childhood onset T1D potentially has a negative effect on educational accomplishments already at the compulsory and upper secondary levels (Dahlquist *et al.* 2007, Persson *et al.* 2013). Future study opportunities may become limited if certain school credentials are needed to apply for further education. Therefore, the early repercussions of T1D may plausibly play a part on future career development and earnings. Although not concerning the entire T1D population, there are studies reporting disadvantages in work opportunities among young adults with T1D (Ingberg *et al.* 1996, Milton *et al.* 2006, Persson *et al.* 2013, Robinson *et al.* 1993). At 29 years of age, young adults with T1D in Sweden were less likely to be gainfully employed than their non-diabetic peers (Persson *et al.* 2013). In particular, the combination of T1D and a lack of upper secondary education seemed to be detrimental to a young adult's work prospects. For unclear reasons, non-diabetic peers lacking the same qualifications were much more likely to have successfully acquired a job (Persson *et al.* 2013).

Challenges in balancing intense T1D self-care and other demands of life are reflected in reports describing difficulties adequately managing T1D in the workplace (Balfe *et al.* 2014, Ruston *et al.* 2013). Employed young adults have reported experiencing difficulties managing T1D adequately in the work environment due to time pressure and the non-routine nature of work (Balfe *et al.*

2014). Long hours, busy schedules and unpredictable work days impede T1D self-management with postponed or skipped meal times, irregular opportunities for blood glucose control and difficulties in taking enough physical exercise. Many seem to compromise and opt for suboptimal self-care when the pressure at work is high. It seems that young adults are especially inclined to deliberately neglect or delay their diabetes management activities in the workplace (Balfe *et al.* 2014).

Due to unsupportive attitudes at work, patients often find it necessary to alter self-management routines to fit their job (Ruston *et al.* 2013). Many employees with T1D feel a need to minimise the visibility of their disease and its disruption to work. Patients may deliberately allow glucose levels to be unnecessarily high to ensure alertness and good performance in demanding situations (Ruston *et al.* 2013). Hypoglycaemic events are particularly avoided by many because of the risk of sudden incapacity and a need for outside assistance. In a study investigating mostly patients with T1D, nearly 75% of the subjects reported maintaining blood glucose voluntarily at an unnecessarily high level in order to minimise the chance of experiencing of hypoglycaemia at work (Ruston *et al.* 2013). Deliberate disregard to self-care needlessly exposes these patients to the effects of prolonged hyperglycaemia. HbA1c variability has also been shown to be an independent risk factor for DR (Hermann *et al.* 2014).

High productivity is in demand in the labour market and poor economic times add to the competitiveness of the workplace. According to an interview study, young adults with T1D often feel guilty or self-conscious of taking time out during work hours to monitor and regulate diabetes (Balfe *et al.* 2014). Sometimes T1D related clinical appointments are skipped due to time pressures at work or a fear of being perceived as being a less productive employee (Balfe *et al.* 2014).

Difficulties in finding adequate time for self-management and the common desire to diminish the visibility of T1D at work potentially increase perceived work related distress. Chronic fatigue has also been reported to be rather prevalent and clinically relevant among the T1D population (Goedendorp *et al.* 2014). Physical, emotional and social effects of T1D can have a substantial impact on the longevity of an individual's active participation in the workforce. High job strain predicts long-term sickness absence and disability pension also in the general population (Laine *et al.* 2009, Virtanen *et al.* 2007, Wang *et al.* 2014).

A study evaluating clinical factors predicting work disability found T1D status, diabetic complications and lower educational attainment to be associated

with an increased risk of unemployment (Von Korff *et al.* 2005). The second multinational Diabetes Attitudes, Wishes and Needs (DAWN) study included a working aged T1D population of 1 368 subjects, 7% of those subjects were unable to work and 13% had retired while 46% held a full-time job (Nicolucci *et al.* 2013). 43% of the subjects not working full-time reported that this was due to T1D related reasons (Nicolucci *et al.* 2013). There are very few high quality studies on work disability focusing solely on patients with T1D, but mixed diabetic populations typically with a T2D predominance, have found evidence of increased work absenteeism, unemployment and early retirement due to diabetes (Breton *et al.* 2013, Von Korff *et al.* 2005).

3 Aims of the study

The purpose of the present study was to evaluate the ophthalmic status and characteristics related to the general well-being of a population-based cohort of paediatric patients with T1D and a population-based cohort of young adults with T1D since childhood. The specific aims were:

1. To compare the prevalence of DR and its risk factors between two similar paediatric cohorts with T1D assessed 18 years apart (I).
2. To study the HRQoL of a young adult cohort with T1D especially in relation to DR and its severity (II).
3. To determine the prevalence and stage of DR in a cohort of young adults with T1D since childhood (III).
4. To assess the social status of a young adult cohort with a long duration of T1D (IV).

4 Materials and methods

4.1 Paediatric cohort

4.1.1 Study subjects

A population-based paediatric cohort was examined for the prevalence of DR and its risk factors in 2006–2007. The cohort consisted of all 5–16 year-old children and adolescents with T1D (n=297) living in the catchment area of the Northern Ostrobothnia Hospital District, Finland on 1 January 2007.

Paediatric patients with T1D in Finland are provided with specialized diabetes care by their respective hospital districts. Regular follow-up visits at Paediatric diabetes clinics take place approximately every three months. The frequent controls most likely facilitate participation also in DR screenings and help in achieving good coverage of the paediatric population.

4.1.2 Methods

Study design

In this observational population-based study, a cross-sectional evaluation of risk factors and prevalence of DR was performed. Fundus photographs were taken in 2006–2007 of all 5–16 year-old children and adolescents with T1D to assess the prevalence and stage of DR. The Paediatric diabetes clinic of Oulu University Hospital was caring for 297 paediatric patients of whom 251 participated in the current study.

Starting from the early 1990s, all paediatric patients with T1D living in the Northern Ostrobothnia Hospital District have been annually screened for DR after T1D duration of five years or at the latest from the age of ten years onward. During the study period, also younger patients were encouraged to attend screening photography to obtain a comprehensive evaluation of the entire paediatric population for research purposes. The paediatric cohort's results on prevalence and risk factors of DR were compared to a similar population-based cohort consisting of patients with T1D of equal age who had attended the Paediatric diabetes clinic 18 years earlier.

The former paediatric cohort of 216 subjects (123 boys and 93 girls) was evaluated in 1989–1990 for prevalence of DR, HbA1c, age at the time of examination and age at T1D onset. A total of 194 subjects attended DR screening and an additional four adolescents were clinically examined during the study period. No diabetic fundus changes were detected in 177 of the subjects, but 21 had developed manifest DR.

The current study was approved by the Ethics Committee of Oulu University Hospital.

Fundus photography

Digital fundus photographs were taken by experienced professional photographers in the Department of Ophthalmology with a CF-60UVI camera. Mydriasis was achieved by topical administration of cyclopentolate 10mg/ml eye drops. Single-field colour and black-and-white macula-centred images of 60° were taken of each eye. The pictures were of high quality due to the absence of significant media opacification in the paediatric cohort.

The digital fundus images were viewed independently by two members of the research group. The inter-rater reliability was good with evaluations of DR differing only with respect to one patient's photographs. In that particular case, the images were re-assessed by both evaluators who then came to a mutual decision on the final classification. DR grading was performed using the modified ETDRS classification (ETDRS research group 1991c).

Risk factors of DR

To assess risk factors of DR, clinical information was collected from Paediatric diabetes clinic's patient records. The control visit closest to the time of fundus photography was selected for gathering the patient data. Age and T1D duration at the time of fundus photography were recorded. HbA1c, blood lipid profile, urinary albumin content and BP values were collected. The patients' gender, stage of puberty according to the Tanner classification, relative height for age and relative weight for height based on national growth charts were also recorded.

4.2 Adult cohort

4.2.1 Study subjects

The population-based adult cohort consisted of young adults with T1D since childhood. In 1989–1990, the same 216 individuals aged 5–16 years had been attending the Paediatric diabetes clinic in the Northern Ostrobothnia Hospital District. This paediatric cohort with T1D was examined for prevalence of DR and its risk factors (Falck *et al.* 1993). Eighteen years later, the same subjects were invited to participate in an extensive re-examination. The young adult cohort was evaluated for characteristics potentially influenced by T1D including the presence and severity of DR, HRQoL and social well-being.

4.2.2 Methods

Study design

The adult cohort was contacted in 2007 to study the effects of a long duration of T1D in a population-based cohort of young adults. In 18 years, the former paediatric cohort living in the catchment area of the Northern Ostrobothnia Hospital District had grown up and dispersed to different locations throughout Finland and abroad. The individuals were contacted by mail and/or phone to invite them to take part in the follow-up study.

The Ethics Committee of Oulu University Hospital approved the study. The contacted subjects were given information about the study protocol according to the Helsinki Declaration. At enrolment, all participants signed an informed consent.

Examination visit

The participants were assigned an examination time and they received questionnaires to complete in advance. Reimbursements were offered for travel expenses. Each examination was performed by one of the three ophthalmologists working in the Department of Ophthalmology designated for the task. The study protocol and agreement to participate were discussed and questionnaires collected.

Best corrected visual acuity (BCVA) was assessed for each eye using the ETDRS chart. The patients underwent an extensive ophthalmic evaluation including biomicroscopic status before and after pupil dilatation and measurements of IOP, refraction power and contrast sensitivity were performed. Each patient was also measured for weight, height and body mass index, BP, pulse and waist girth. Patients' current HRQoL was estimated using the self-administered 15D-instrument. Digital fundus photographs were taken by photographers in the Department of Ophthalmology. Laboratory tests were taken to evaluate glycaemic balance (HbA1c), cholesterol level (S-kol, S-HDL-kol, S-trigly and S-LDL-kol) and microalbuminuria (U-alb/krea). Each individual's social, educational and employment history and status were determined with a questionnaire.

Social status questionnaire

The questionnaire concerning social aspects of the patients' lives was designed specifically for the purposes of this study. The questionnaire asked about the year of completing Finnish 9-year compulsory schooling, education after compulsory schooling, work history and current work status, marital status, the years of birth of children, smoking habits, prescribed medications, details of diabetes care and personal opinions concerning diabetes counselling and care.

The questionnaire was filled in by the patient either at home or during the examination visit. The patients who agreed to take part in the study but opted not to attend the examination, filled in and mailed the questionnaire to the investigators.

15D The health-related quality of life instrument

The 15D instrument was used to assess HRQoL of the young adult cohort. 15D is a generic (non-disease-specific) and comprehensive questionnaire designed for adults and adolescents over 15 years of age. The questionnaire is self-administered and consists of 15 statements concerning different aspects of health. Each statement is followed by five alternative answers depicting different degrees of health or illness. The most suitable alternative of the five answers is chosen by the patient. The instrument addresses 15 dimensions regarding an individual's perception of mobility, vision, hearing, breathing, sleeping, eating, speech,

excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity.

The resulting single index score (15D score) is a value on a 0–1 scale. The figure is generated using a set of utility or preference weights. The index value of 1 indicates perfect health while 0 equals being dead (Sintonen 2001). On average, people can feel a change or difference of $\geq | 0.03 |$ in the 15D score, making alterations of an equivalent magnitude clinically important (Sintonen 1994). The 15D can also be viewed as a profile. In article II, the young adults' HRQoL was compared to that of an age- and gender-standardised Finnish control population from the previous Terva study (Arinen *et al.* 1998).

4.2.3 Fundus photography

Digital fundus photographs were evaluated to determine the prevalence and stage of DR. The images were taken in the Department of Ophthalmology at Oulu University Hospital by trained photographers with years of experience in ophthalmic imaging. Mydriasis was achieved with topical instillation of tropicamide and phenylephrine hydrochloride eye drops.

The images were taken with a Canon CF-60DSi Digital Mydriatic Fundus Camera. Colour and black-and-white images of 60° field were taken from both eyes of each participant. Two sets of pictures were taken per eye with one image centred on the macula and the other on the optic disc.

The fundus images were categorised into five stages of DR according to a screening recommendation of the Finnish Current care guideline (Table 3). If the stage of DR was not similar in both eyes of the patient, the classification was recorded according to the condition of the more advanced eye.

Table 3. International clinical classification system for severity of DR was used to evaluate the stage of DR in the adult cohort.

Severity of DR	Fundus changes
No DR	No changes
Mild non-PDR	Microaneurysms
Moderate non-PDR	More than microaneurysms, less than severe non-PDR
Severe non-PDR	Any of the following: >20 intraretinal haemorrhages in all four quadrants definite venopathy in at least two quadrants prominent IRMA in at least one quadrant No sign of PDR
PDR	One or more of the following: neovascularisation preretinal or vitreous haemorrhage tractional retinal detachment fibrovascular growth

4.3 Statistical methods

X^2 test and independent-samples t-test were used for analysing the differences between the groups. Risk factors of DR were evaluated using logistic regression. Fisher's exact test, independent samples t-test, Mann-Whitney U test were used when appropriate. P-value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS for Windows (version 18.0, SPSS Inc., Chicago, Ill., USA). Biostatisticians were consulted when needed.

5 Results

5.1 Paediatric cohort with type 1 diabetes

The population-based paediatric cohort consisting of 297 children and adolescents with T1D were evaluated for prevalence of DR and its risk factors. The cohort's 158 boys and 139 girls were born in 1990–2001 with a mean age of 11.9 years and a mean T1D duration of 4.9 years at the time of the examination (Table 4). A total of 251 (85%) of the 297 subjects attended fundus imaging as requested during 2006–2007. In addition, 34 patients with a short duration of T1D or young age were photographed for the first time in 2008. Seven children had attended DR screening in 2005 and did not take part again until 2008. Five children had not participated in any DR screening by the end of 2008.

The results of the paediatric cohort screened for DR were compared to a similar population-based cohort study performed in 1989–1990 (Falck *et al.* 1993). The previous cohort's 216 paediatric patients consisted of 123 boys and 93 girls with a corresponding mean age of 11.8 years and a disease duration of 4.9 years (Table 4). The examination was attended by 194 (90%) of 216 subjects.

Table 4. Demographics of the paediatric cohorts.

Parameters	Cohort of 1989			Cohort of 2007		
	Boys	Girls	All	Boys	Girls	All
N (%)	123 (57)	93 (43)	216 (100)	158 (53)	139 (47)	297 (100)
Age (mean±SD)	11.9±3.3	11.7±3.1	11.8±3.2	11.9±3.1	11.8±3.2	11.9±3.1
Age at T1D diagnosis (mean±SD)	6.8±3.8	7.0±3.7	6.9±3.8	7.1±3.8	6.8±3.7	7.0±3.7
Duration of T1D (mean±SD)	5.0±3.7	4.8±3.5	4.9±3.6	4.8±3.1	5.0±3.4	4.9±3.2
HbA1c mmol/mol (%) (mean±SD)	68±13 (8.4±1.6)	73±15 (8.8±1.8)	70±14 (8.6±1.7)	74±13 (8.9±1.6)	74±12 (8.9±1.5)	74±12 (8.9±1.5)
Subjects with DR N (%)	9 (7)	12 (13)	21(10)	12 (8)	23 (17)	35 (12)
HbA1c of DR group (mean±SD)	89±14 (10.3±1.6)	89±13 (10.3±1.5)	89±13 (10.3±1.5)	92±19 (10.6±2.2)	81±14 (9.6±1.6)	85±16 (9.9±1.9)
HbA1c of non-DR group (mean±SD)	66±12 (8.2±1.5)	69±14 (8.5±1.7)	67±13 (8.3±1.6)	73±12 (8.8±1.4)	72±12 (8.7±1.4)	73±12 (8.8±1.4)

5.1.1 Prevalence of diabetic retinopathy and risk factors

Of the paediatric cohort screened in 2006–2007, 33 patients had developed manifest DR in one or both eyes. The detected fundus changes were unilateral in 70% (23/33) of the subjects. DR was classified as mild in all cases with only microaneurysm(s) in eight patients and/or small retinal haemorrhage(s) in 25 patients. The remaining 218 subjects had no detectable DR in fundus images.

None of the 34 subjects first photographed during 2008 had DR. They were some of the youngest patients (8.8 ± 2.2 years) attending the screening and they also had a shorter duration of T1D (3.9 ± 1.8 years).

From the seven children screened in 2005 and again in 2008, five had normal fundus images. One girl had DR both times and another girl had normal fundus photographs in 2005, but had developed DR by 2008. The prevalence of DR out of the 297 subjects was 11% at the minimum and 12% assuming the two girls photographed in 2008 both had DR already at 2007. DR became manifested at an earlier age in girls than in boys.

The mean HbA1c of the years with T1D was 78 mmol/mol (9.3%) among the subjects with DR compared to 67 mmol/mol (8.3%) in those without DR ($p=0.001$). The latest HbA1c values were 73 ± 12 mmol/mol ($8.8\pm 1.4\%$) in the group without DR (Table 4). With respect to the group with manifest DR, the patients with only microaneurysm(s) detected on fundus images had the latest HbA1c values of 73 ± 8 mmol/mol ($8.8\pm 1.0\%$), while those who presented with retinal haemorrhage(s) had poorer glycaemic control with the latest HbA1c values of 89 ± 3 mmol/mol ($10.3\pm 0.4\%$).

The characteristics predicting the development of DR in the present study were duration of T1D ($p<0.001$), age ($p<0.001$), higher mean HbA1c during the years of T1D ($p<0.001$), latest HbA1c value ($p=0.001$), onset of puberty ($p<0.001$) and female gender ($p=0.016$). A binary logistic forward stepwise regression analysis estimated age (OR 1.2, 95% CI 1.0 to 1.4), duration of T1D (OR 1.3, 95% CI 1.1 to 1.5), mean HbA1c of the years with T1D (OR 2.1, 95% CI 1.5 to 3.1) and gender (OR 2.3, 95% CI 1.0 to 5.4) could explain 35% of DR. Unrelated factors included relative weight for height ($p=0.166$), height SDS ($p=0.980$) and albuminuria ($p=0.584$).

5.1.2 Comparison of the paediatric cohorts

The number of children and adolescents with T1D in the catchment area of the Northern Ostrobothnia Hospital District had increased by 38% during the past 18 years. There was a change from 216 patients in the former study in 1989–1990 to the current cohort's 297 patients evaluated in 2006–2007. The mean age of the subjects and the duration of T1D were similar between the two paediatric cohorts. Five patients from the latter study and 22 patients from the former study did not attend DR screening.

The prevalence of DR in the entire paediatric cohort studied in 2006–2007 was 12% (35/297); 17% (23/139) in females and 8% (12/158) in males. In the previous study in 1989–1990, the overall prevalence of DR was 10% (21/216) with 13% of females and 7% of males having developed DR.

The current cohort's overall prevalence of DR was quite similar to that of the former cohort. However, among girls DR was more frequently detected than in the previous cohort. In both cohorts, DR was more prevalent in girls than in boys, although there were no significant gender-related differences in their HbA1c values. Risk factors of DR had remained mostly unchanged: DR was associated with a longer duration of T1D, older age, higher HbA1c, female gender and onset of puberty. The comparison of the HbA1c values of the two cohorts revealed that the metabolic control of the paediatric patients had not improved during the 18-year study period.

5.2 Adult cohort with childhood-onset type 1 diabetes

The population-based adult cohort originally consisted of 216 paediatric patients living in the catchment area of the Northern Ostrobothnia Hospital District in 1989–1990. During the re-examinations in 2007, 208 subjects of the original cohort were alive. Eight patients (4%), three women and five men, had died during 1993–2007 at the age of 17–32 years. One patient had died of vascular complications of T1D and another had severe multiple sclerosis. Two of the deceased had been mentally retarded.

A total of 172 (80%) subjects of the original cohort of 216 were successfully contacted and of these, 108 (50%) patients attended the extensive re-examination in the Department of Ophthalmology of Oulu University Hospital in 2007. Additionally, 64 (30%) filled in some or all of the questionnaires and gave permission to access their medical records but did not attend the examination

visit. The remaining 36 (17%) subjects could not be reached or refused to participate.

At the time of the re-examination, the still living cohort of 118 men and 90 women was 30 ± 3 years of age (range 22–35 years) with 23 ± 4 years (range 17–32) of T1D duration. The diagnosis of T1D had been made on average at the age of 7 ± 4 years (range 0–15 years). The 172 participants and the 36 non-participants of the surviving cohort did not differ significantly in terms of age (30 ± 3 years vs. 30 ± 4 years, $p=0.299$) or duration of T1D (23 ± 4 years vs. 22 ± 4 years, $p=0.495$).

Among the subjects attending and not attending the original DR screening in 1989–1990, the 18-year mortality was 2% (3/198) and 28% (5/18), respectively.

5.2.1 Prevalence of diabetic retinopathy

The prevalence and stage of DR were determined in 172 of the cohort's young adults in 2007. These subjects represented 80% of the original paediatric cohort. In 131 cases, the stage of DR was assessed from fundus photographs taken at the examination visit. Additionally, the DR status of 41 subjects was determined from either fundus photographs or from the written patient records detailing the results of a clinical fundus examination performed at the subject's current healthcare provider's office. Of the 8 deceased subjects, one had been diagnosed with PDR but none were known to be visually impaired.

The fundus photographs taken in the Department of Ophthalmology at Oulu University Hospital were evaluated independently by two ophthalmologists masked to the patients' identities. Inter-rater agreement was good with 96% (126/131) of evaluations being congruous between the two ophthalmologists. In five cases with grading disagreement, the pictures were re-evaluated by a third ophthalmologist before making the final classification.

In the fundus images of 11/172 (6%) subjects (6 women and 5 men), there were no signs of DR. The remaining 161 (94%) subjects (91 men and 70 women) had manifest DR in one or both eyes. PDR had developed in 60 (35%) subjects (33 men and 27 women). No significant difference was detected between the genders in the prevalence or severity of DR ($p=0.356$).

Table 5. Demographics of the young adult cohort and DR results of the extant 208 cohort subjects.

Parameters	Men	Women	All
Original cohort N (%)	123 (57)	93 (43)	216 (100)
Deceased N (%)	5 (2)	3 (1)	8 (4)
Extant cohort N (%)	118 (55)	90 (42)	208 (96)
Mean age of extant cohort (mean±SD)	30±3	30±3	30±3
Duration of T1D (mean±SD)	23±4	23±4	23±4
Subjects with no DR N (%)	5 (4)	6 (7)	11 (5)
Subjects with DR N (%)	91 (77)	70 (78)	161 (77)
Non-proliferative DR N (%)	44 (37)	38 (42)	82 (39)
Pre-proliferative DR N (%)	14 (12)	5 (6)	19 (9)
PDR N (%)	33 (28)	27 (30)	60 (29)
Unknown fundus status N (%)	22 (19)	14 (16)	36 (17)

5.2.2 Health related quality of life

Information on the HRQoL of the adult cohort was gathered using the self-administered 15D instrument. A total of 123 patients filled out the 15D, representing 56% of the original cohort. The subjects (74 men and 49 women) were 29±3 years of age with T1D duration of 23±4 years at the time of 15D evaluation. DR had been diagnosed in 115 (93%) subjects taking part in HRQoL assessment; of these, 38 had developed PDR and the remaining 77 subjects had less advanced DR. Fundus images of six (5%) patients had no signs of DR, and the ophthalmic status of two subjects remained unknown.

The mean 15D score of the young adult cohort indicated good HRQoL and did not differ statistically significantly from the age- and gender-matched Finnish control population (0.954±0.062 vs. 0.964±0.052; p=0.085). The difference in mean 15D score was not statistically significant between men and women (0.960±0.067 vs. 0.944±0.052; p=0.184).

A comparison was performed between the subgroup diagnosed with PDR and the other group with less severe or no DR (Fig. 6). The subgroup with PDR had a significantly lower mean 15D score when compared to the subjects with less advanced fundus status (0.931±0.086 vs. 0.965±0.044; p=0.026). Vision, usual activities, mobility and sexual activity were the dimensions which displayed a significant difference to the disadvantage of the PDR group (Fig. 6). The individuals without PDR scored equally well on all dimensions of the 15D as the control group.

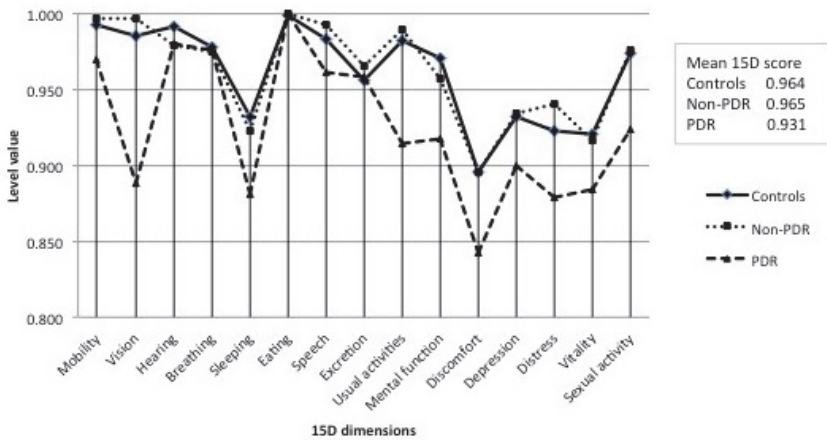


Fig. 6. Comparison of 15D results subdivided according to the severity of DR.

BCVA was assessed in all but nine subjects for whom there was HRQoL information. The majority of the cohort had good VA irrespective of diabetic fundus changes. In all, 60% (74/123) of the subjects had BCVA of ≥ 1.0 Snellen and 86% (106/123) had BCVA of ≥ 0.5 Snellen in both eyes. Three individuals had one blind eye due to DR, with the other eye’s BCVA ranging from 0.1–0.4 Snellen. One individual was visually impaired according to the WHO classification, but had nonetheless a 15D index score of 0.930.

5.2.3 Social well-being

A total of 136 (63%) subjects of the original 216 took part in the evaluation of the cohort’s social well-being by filling in the provided questionnaires. The participants (78 men and 58 women) were 30 ± 3 years of age with a mean T1D duration of 23 ± 4 years. The subject’s mean age at T1D onset had been 7 ± 4 years, ranging from 11 months to 16 years. Eighty (37%) individuals of the original cohort, including eight deceased subjects, were not represented in the acquired data.

PDR had developed in 42 of the 136 participating subjects with their mean age of 31 ± 3 years. Seven evaluated subjects had no manifest DR and current fundus information was not available in two subjects. The cohort was divided into the PDR group (31%) i.e. subjects with proliferative fundal changes and the non-

PDR group with subjects having less severe (63%) or no manifest DR (5%). The age at T1D onset did not differ significantly between the PDR and non-PDR groups ($p=0.865$, Mann-Whitney U test).

Of the 136 subjects, 97 (71%) reported being married or cohabiting. The percentage was higher among the cohort subjects than the Finnish general population of the same age. Thirty-one (23%) participants were single and eight (6%) were divorced.

Sixty subjects, representing 44% of males and 45% of females, were parenting a total of 119 children. Twenty-six females had 45 children and 34 males had 77 children. Three children belonged to a couple both of whom were participating in the study. Twenty-seven subjects had one child, 26 subjects had two or three children and seven subjects had four to nine children. Seven individuals were expecting at the time of evaluation with one of them becoming a parent for the first time.

Among the 23–24 year-olds and the 25–29 year-olds, the cohort subjects were more commonly parenting children compared to the Finnish general population. In the age-group of 30–34 years, the difference had levelled off. Of the 60 subjects parenting children, 20 (33%) were diagnosed with PDR while four (7%) had no signs of DR. Similarly, for the subjects without children, 22 (29%) had developed PDR and three (4%) had no detectable DR in fundus evaluation.

The highest attained educational degree of 12 (9%) of the 136 subjects was a university degree. A degree from a university of applied sciences was held by 45 (33%) and 61 (45%) had finished vocational school. Ten (7%) were full-time students. Seven (5%) of the cohort subjects reported not having undertaken any further education after completing nine years of compulsory comprehensive schooling.

A full-time job was held by 63 of 92 subjects (68%) of the non-PDR group, and 25 of 42 (60%) of the PDR group. Four (4%) vs. six (14%) subjects were unemployed in the non-PDR and the PDR group, while none vs. five (12%) were on full-time pension. Additionally, one subject in the PDR group was on partial pension. The remaining subjects were on maternity leave, studying or working part-time.

All of the cohort subjects on partial or full-time pension had decreased VA. Four of these six subjects fulfilled the criteria of visual impairment with BCVA <0.3 Snellen. Additionally, one subject on maternity leave was visually impaired. None of the unemployed young adults or the subjects lacking secondary education had significantly reduced VA.

The subjects with PDR were equally likely to have a spouse ($p=0.349$) and children ($p=0.580$) as the patients with less severe or no diabetic fundus changes. Tertiary education had been pursued as often by subjects in both PDR and non-PDR groups ($p=0.131$). However, the individuals with PDR were less likely to have finished secondary education ($p=0.012$). The patients in the PDR group were also significantly more likely to be left outside of working life ($p<0.001$) due to unemployment or retirement.

6 Discussion

An increasing number of children are being exposed to the effects of T1D from an early age due to the globally rising incidence of the disease and the declining age at onset (Borchers *et al.* 2010, Dahlquist & Mustonen 2000, DIAMOND Project Group 2006, Harjutsalo *et al.* 2008, Patterson *et al.* 2009, Patterson *et al.* 2012). In Finland, the Current care guidelines and continuous education of multidisciplinary diabetes teams set the standard for T1D care (Diabetes: Current care guideline 2013). Even though diabetes care is well organised and affordable in Finland, the patient's motivation and adherence to self-care remain key factors in successful T1D management. The complexity of the task leads to various degrees of success which may in part be evaluated by the frequency of early and advanced diabetic complications.

There is still no means of preventing this chronic disease. However, intensive research has achieved moderate improvements in T1D care even during the past decades (Giani *et al.* 2015). These developments have allowed medications to be more precisely adjusted to suit individual needs, overall treatment modalities have improved and support is readily available from multidisciplinary diabetes teams. Advances in T1D care increase the likelihood of reaching treatment targets and delaying the development of diabetic complications. Improved disease outcome potentially further assists in achieving and maintaining good QoL and optimal social well-being.

6.1 Prevalence and risk factors of diabetic retinopathy in children (Study I)

The population-based paediatric cohort evaluated for DR in 2007 in the catchment area of the Northern Ostrobothnia Hospital District attended regular follow-up visits at the Paediatric diabetes clinic of Oulu University Hospital at three month intervals (Kubin *et al.* 2011). The cohort was compared to an earlier population-based cohort of children and adolescents from the same district studied 18 years previously in 1989–1990 for DR and its risk factors (Falck *et al.* 1993).

The number of paediatric patients with T1D had increased in the catchment area of the Northern Ostrobothnia Hospital District by over one third during the study period. This increase clearly surpasses concurrent population growth of the region (11%) during the time period 1990–2006 (Statistics Finland 2011) and

illustrates the continually growing incidence of T1D among the Finnish paediatric population.

The glycaemic control of the paediatric cohort examined in 2007 was not statistically different from the cohort studied 18 years earlier. Changes made to the care of T1D during 1989–2007 appear to have been inadequate to generate a significant difference in the HbA1c levels between the population-based cohorts (Kubin *et al.* 2011). One could have anticipated a moderate improvement in the more recent results due to the advances in T1D care occurring during the study period. However, some of the most significant treatment advances since the invention of insulin were made around the 1980s i.e. the introduction of MDI and CSII therapy and to some extent both cohorts had enjoyed these benefits at the time of their respective HbA1c evaluations. The treatment methods for each individual patient were not recorded for this study and therefore the difference in utilization of MDI or CSII between the two cohorts is unknown.

The novel treatments of the 1980s have long since become established as standard care and glycaemic results may have reached a relative plateau with mainly modest improvements being detected over time. More recent developments including the intensified multidisciplinary approach to care, continued development of insulin analogues and continuous patient/family education have been advocated as ways to facilitate further improvements in the HbA1c results (Giani *et al.* 2015). Although the tools needed for achieving fairly optimal glycaemic balance are available and widely in use, it is the difficulties encountered in complying day in - day out, with T1D related self-care demands which are likely to represent the greatest impediment to maintaining normoglycaemia.

Unlike the current study, some reports have described improved glycaemic results among paediatric populations during a similar time frame. A study examining 11–17 year-old Australian adolescents with 2–5 years' duration of T1D reported that the median HbA1c had improved from 71 mmol/mol (8.7%) in 1990 to 66 mmol/mol (8.2%) in 2002 in parallel with the increased total daily insulin dose and injections per day (Cho *et al.* 2011). In agreement, the prevalence of DR declined from 16% to 7% (Cho *et al.* 2011). Another study examining 12–20 year-old Australians detected a reduction of median HbA1c from 76 mmol/mol (9.1%) during the period 1990–1994 down to 69 mmol/mol (8.5%) during 2005–2009 with the use of MDI and CSII increasing concurrently from 17% to 88% (Downie *et al.* 2011). Similarly, the prevalence of DR was observed to decline from 53% to 12% during that time period (Downie *et al.* 2011).

A nationwide population-based study in Denmark found that HbA1c values had declined in a paediatric population with T1D from a mean HbA1c of 76 mmol/mol (9.1%) in 1997 to 66 mmol/mol (8.2%) in 2006 (Svensson *et al.* 2009). The linear decrease in HbA1c was -0.08% per year and this was reached without increasing the rate of severe hypoglycaemic incidents. The improvement in glycaemic balance was associated with an increased number of self-monitoring of blood glucose over the years (Svensson *et al.* 2009). While the Danish study indicated a clear HbA1c improvement of 10 mmol/mol (-0.9%) during the 10-year study period, the latest HbA1c values between the cohorts of this present study had slightly, although insignificantly, increased by 4 mmol/mol ($+0.3\%$) in the elapsing 18 years.

Concurrently to improvements in glycaemic balance, multiple studies have shown promising results on reducing the prevalence of DR after increased implementation of new treatment modalities since the 1980s (Henricsson *et al.* 2003, Lecaie *et al.* 2006). However, in this study, the overall prevalence of DR among children and adolescents with T1D remained nearly unchanged during the 1989–2007 study period. In both cohorts, girls had developed DR more frequently and at an earlier age than boys (Kubin *et al.* 2011). Girls even experienced a slight increase in the prevalence of DR (12.9% in 1989 vs. 16.5% in 2007), although the majority of subjects displayed no diabetic fundus changes. The static prevalence of DR between the two paediatric cohorts examined 18 years apart reflects the unchanged glycaemic balance. The challenges in improving T1D management and compliance to lower the frequency of microvascular complications at a young age still remain despite the promising options offered by medical technology and therapeutics.

Despite the higher numbers with manifest DR, girls had on average slightly better HbA1c values than boys in both examined cohorts (Kubin *et al.* 2011). Female gender remains a clear risk factor for DR among the paediatric population. The difference in DR manifestation may be largely explained by the earlier occurrence of puberty with its associated hormonal changes affecting insulin metabolism (Amin *et al.* 2005). Overall, the risk factors of DR have not changed significantly among the population-based paediatric cohorts during the study period of 1989–2007 (Kubin *et al.* 2011).

All detected cases of DR in the two paediatric cohorts of this study were mild. Young age is a significant predictor of prevalence and severity of DR, with diabetic complications being uncommon before puberty (Falck *et al.* 1993). Although the age at T1D onset is declining globally, the prevalence of DR among

paediatric population does not seem to be markedly affected. The earlier onset of T1D will increase the mean disease duration at any given age, but according to the current understanding, the influence of prepubertal years on the development of diabetic complications is modest (Olsen *et al.* 2004).

6.2 Prevalence and risk factors of diabetic retinopathy in young adults (Study III)

The development of DR and other diabetic complications is influenced by a variety of modifiable and non-modifiable risk factors. Successfully executed self-care remains the patient's most efficacious way to delay or prevent the manifestation of T1D related complications. However, regardless of modifiable risk factor management, the duration of T1D significantly increases the risk of DR and other microvascular complications among all age groups (DCCT Research Group 1993).

The cohort of young adults with T1D since childhood was evaluated for DR in 2007 (Hautala *et al.* 2014b). After an average of over two decades of living with T1D, this cohort displayed a high prevalence of DR with the vast majority of evaluated subjects having developed manifest retinal microangiopathy (Hautala *et al.* 2014b). The result was anticipated in view of the fact that DR becomes almost inevitable with a long duration of T1D. In a similar manner, 97% of the WESDR population and 92% of the more recent WDRS population had manifest DR after a T1D duration of 20 years (LeCaire *et al.* 2013).

T1D rather consistently causes DR at some point during the disease course regardless of achieved HbA1c levels. However, the severity of DR is more likely to diminish due to the currently achievable improvements in glycaemic balance, as has been demonstrated in the WESDR and WDRS cohorts (LeCaire *et al.* 2013). These studies showed that the severity of DR, in addition to the aforementioned prevalence, was more favourable in the later WDRS cohort after a T1D duration of 20 years (LeCaire *et al.* 2013). The positive outcome was largely attributed to the intensified care of T1D. The DCCT has also reported a delay in onset and progression of DR in both adult and adolescent cohorts (DCCT Research Group 1993, DCCT/EDIC Research Group 2000, White *et al.* 2010).

In the current adult cohort investigated in 2007, PDR was diagnosed in 35% of study subjects compared to 36% of the WESDR and 11% of the WDRS cohorts after 20 years of T1D duration. In the current study, 6% of patients showed no signs of DR (Hautala *et al.* 2014b). In comparison, 3% of the WESDR cohort and

8% of the WDRS cohort had no DR after a T1D duration of 20 years (LeCaire *et al.* 2013).

There was no significant difference in the prevalence of DR between genders in the young adult cohort (Hautala *et al.* 2014b). The higher prevalence of DR in females during adolescence resulting from gender-related developmental characteristics, appeared to have evened out by early adulthood. However, also conflicting results have been published, with some studies reporting a predominance of DR in females and other studies stating that it is more common in males (Hammes *et al.* 2011, Minuto *et al.* 2012).

The severity of DR was similar between men and women in the current cohort (Hautala *et al.* 2014b). In general, the severity of DR and diabetes induced vision loss have decreased over time with intensified management of T1D and improved possibilities to treat severe fundus pathologies. However, regular screening for DR remains vital for preventing the T1D related loss of vision. Screening for DR has proved to be highly cost-effective (Javitt & Aiello 1996, Li *et al.* 2010b, Pajunpää 1999). Successfully executed DR screening and chain of care have significant economic importance considering the long-term cost attributable to severe visual impairment or blindness (Pajunpää 1999).

6.3 Health related quality of life and type 1 diabetes (Study II)

T1D can have complex repercussions on an individual's physical and mental well-being, influencing also the HRQoL significantly. The psychological burden of T1D can be stressful for patients regardless of the presence and severity of related complications or comorbidities. The readiness to come to terms with the T1D diagnosis and the ensuing changes in life differs between individuals (Chaplin *et al.* 2009). Mostly patients are assumed to adapt adequately to the demands of their chronic illness. However, some individuals may feel persistently more burdened by the disease and keep struggling with the demanding self-care routines. Difficulties in adaptation may predict suboptimal glycaemic balance and possibly lead to the premature development of diabetic complications and reduced HRQoL (Samuelsson *et al.* 2014).

The mean 15D score of the young adult cohort with a long duration of T1D was equal to that of the age- and gender-standardised population (Hannula *et al.* 2014). The result reflects the good overall health and relatively young age of the cohort despite childhood onset T1D. It could be speculated that also ease of access to public healthcare services and minimal personal costs of T1D related

expenditures are among the factors maintaining good disease control and HRQoL. Elsewhere, financial issues and health system bureaucracy have been reported as complicating factors in T1D management (Balfe *et al.* 2013).

Reaching and maintaining optimal self-care targets can be demanding and the recommendations are rarely fully met despite current treatment modalities (Eeg-Olofsson *et al.* 2007). However, DR commonly develops after a long disease duration, even regardless of satisfactory glycaemic balance. The young adult cohort had a high prevalence of DR (93%) after two decades of T1D duration (Hannula *et al.* 2014). The majority of the subjects had unaffected VA despite manifest DR, and only one patient was visually impaired. Despite the good overall HRQoL in this cohort, clear differences in the 15D index were detected between the subgroups according to the severity of DR. Patients with PDR reported significantly lower HRQoL values than the rest of the cohort with milder or no DR (Hannula *et al.* 2014).

The 15D is a generic instrument and therefore the difference detected between subgroups' 15D scores may be influenced also by factors other than T1D. The reduced 15D score observed in the group with PDR can likewise reflect a broad range of T1D related problems, not solely ophthalmic difficulties. Accordingly, the only patient with a bilateral visual impairment had a 15D score of 0.930 while the entire PDR group, mostly with much better visual function, scored equally well with an 15D score of 0.931 (Hannula *et al.* 2014). The microvascular complications of T1D all have similar risk factors, and the patients with PDR are likely to have additional diabetic complications further contributing to their disease burden. In the FinnDiane Study, 53% of the subjects who had received laser treatment for DR had also developed comorbid diabetic nephropathy (Ahola *et al.* 2010).

The dimensions significantly reducing the 15D score of the PDR group were vision, usual activities, mobility and sexual activity (Hannula *et al.* 2014). The alternatives describing current vision in the 15D questionnaire range from having normal vision to blindness. T1D related visual problems can vary from benign shifts in refractive power and a decrease in contrast sensitivity to bilateral blindness due to PDR. The visual function, including VA, contrast sensitivity and visual fields, can be negatively influenced by DR as well as treatment procedures such as fundus laser photocoagulation.

The results of the French DAWN2 survey showed T1D to have a negative impact on the patients' QoL (Reach *et al.* 2015). In comparison to the current cohort, the DAWN2 patients were older, with almost two thirds being ≥ 40 years

of age. In all, 78% of the DAWN2 subjects with T1D estimated that diabetes had exerted a “slightly to very negative impact” on their physical health (Reach *et al.* 2015). Over half of the patients also reported leisure activities, emotional well-being and work or studies having been “slightly to very negatively” affected by T1D. The difference in QoL between the French survey and the cohort examined in article II may be largely explained by the younger age and possibly better overall health of the young adult cohort. HRQoL has been known to decline with advancing age irrespective of whether diabetic complications have developed (Ahola *et al.* 2010).

The HRQoL of the FinnDiane Study population, consisting of over a thousand patients with mean age of 46 ± 12 years and T1D duration of 29 ± 13 years, was evaluated with the 15D instrument during 2004–2008 (Ahola *et al.* 2010). The mean 15D score of the FinnDiane Study population was 0.899 ± 0.095 being significantly lower than that of the current young adult cohort’s mean 15D of 0.954 ± 0.062 . The difference is plausibly in part related to older age and the longer duration of T1D of the FinnDiane population. The 15D result did not statistically differ according to gender in either study. Approximately one third of the subjects in the FinnDiane Study as well as in the present study had developed PDR, with both subgroups having reduced scores on dimensions of mobility, vision and usual activities (Ahola *et al.* 2010, Hannula *et al.* 2014).

Interestingly, the presence of PDR did not negatively effect the overall HRQoL in the FinnDiane Study (Ahola *et al.* 2010). The PDR subgroup of the current study had a reduced mean 15D score even though the subjects were significantly younger than those examined in the FinnDiane Study. However, all patients having received retinal laser treatment were classified as having PDR in the FinnDiane Study (Ahola *et al.* 2010). Laser treatment may be administered prophylactically in the pre-proliferative stages of DR or in other conditions not affecting visual function at that time. Categorizing patients with less severe DR into the PDR group presumably underestimates the negative effect of PDR on HRQoL.

It takes determination and perseverance to optimally manage T1D over a life time. The disease poses a life-long threat to a patient’s HRQoL with intricate self-care routines and common complications and comorbidities (Diabetes: Current care guideline 2013). Were the current cohort to be re-evaluated again in 20 years, the 15D score would most likely be less favourable with accumulating and advancing diabetic complications as well as ageing. The fewer complications and comorbidities that have developed, the fewer disease related disruptions to daily

functioning can be expected. Today in the developed countries, the course of the disease is no longer defined by lack of means or knowledge but rather by the individual's treatment adherence and motivation for self-care. New treatment modalities posing less self-care demands on the patient will most likely be required before the entire T1D population will be able to achieve radical improvements in disease management and to retain good HRQoL throughout their lives.

6.4 Social well-being and type 1 diabetes (Study IV)

T1D may exert a far-reaching impact on several facets of a patient's life including cognitive development, academic performance, achievements in worklife and overall QoL. As a result, T1D can potentially influence an individual's major life decisions and social achievements. The majority of young adults with T1D are productive members of the workforce, actively participating in society and managing their illness well as demonstrated in the population-based young adult cohort (Hannula *et al.* 2015). Nevertheless, a minority can experience substantial difficulties in adapting to the complex self-care routines and potential impairments caused by the chronic illness.

One third of the cohort's young adults with childhood onset T1D had developed PDR despite having access to well-organised diabetes care (Hannula *et al.* 2015). When the subjects in the PDR group were compared to those with milder or no DR, some negative associations were found between PDR and certain aspects of social performance. The individuals with PDR had more frequently dropped out of the labour market due to unemployment or retirement (Hannula *et al.* 2015). Additionally, the subjects in the PDR group were less likely to have received secondary education than the other young adults in the cohort.

The combination of a low level education and increased probability of not being an active member of the workforce is likely to reduce annual income in the PDR group and potentially interfere with these individuals' socioeconomic status. This hypothesis was left without confirmation as income was not assessed in the current study. Encouragingly, the young adults in the PDR and non-PDR groups were equally likely to have received tertiary education and the subjects with PDR were almost equally likely to be in full-time employment as the others in this cohort (Hannula *et al.* 2015).

The correlation found between PDR and suboptimal social performance might in part indicate overall inferior life management skills in some individuals

e.g. manifesting in rapidly advancing complications of T1D and poorer educational achievements. T1D related microvascular complications are rarely sufficiently severe during the late teenage years to cause any significant hindrance to studying. Therefore the difference in frequency of secondary education is unlikely to be caused solely by impairments related to diabetic complications. However, T1D has been associated with increased school absenteeism (Milton *et al.* 2006, Wodrich *et al.* 2011) and slight deficits in neuropsychological performance (Naguib *et al.* 2009). These can be some of the reasons negatively influencing an individual's academic performance and later restrict also prospects for higher education and future success in the labour market.

It has been reported that work disability is significantly more common among individuals with diabetes compared to a non-diabetic population (Mayfield *et al.* 1999, Von Korff *et al.* 2005). With respect to the entire population-based cohort, 12% of the young adults with T1D were either unemployed or retired (Hannula *et al.* 2015). In comparison, 8% of Finnish 30-year-old population (n=67 516) were concurrently in a similar position with 3 977 being unemployed and 1 215 receiving some kind of retirement pension (Statistics Finland 2015). A French study, evaluating young adults with T1D, found a higher frequency of unemployment in women although their education level was similar to the general population (Mellerio *et al.* 2015).

T1D has long been associated with reduced fertility and smaller family size (Jonasson *et al.* 2007, Sjoberg *et al.* 2013, Wiebe *et al.* 2014). Most likely improvements in T1D management have made female subfertility less evident in the more recent birth cohorts (Jonasson *et al.* 2007, Sjoberg *et al.* 2013). In the current population-based cohort, the young adults with T1D were at least as likely to have children as the general population suggesting good overall health despite childhood onset T1D (Hannula *et al.* 2015). The younger subjects of the cohort were even more likely to have children than the Finnish general population of a similar age, although in the age group of 30–34 years, this difference was no longer present (Hannula *et al.* 2015). No dissimilarities in the frequency of parenting were found between the females and the males of the current cohort.

Modern T1D treatment usually maintains physical well-being at a level which allows most young women to safely consider pregnancy (Finnish Diabetes Association 2012). However, women with T1D are generally advised not to needlessly postpone having children because with increased age and T1D duration, difficulties in conceiving and the risks related to advancing diabetic complications may increase (Finnish Diabetes Association 2012). All diabetic

females of reproductive age are encouraged to plan pregnancies and to attend preconception counselling to evaluate possible risks and optimize care of T1D in advance (Diabetes: Current care guideline 2013, Finnish Diabetes Association 2012). The encouragement to have children at an early age may in part explain why the younger cohort subjects had children more frequently than the general population of the same age.

According to the present study, PDR did not compromise the likelihood of having a family in the young adult cohort with long duration of T1D. The young adults investigated here had formed meaningful relationships and were parenting children approximately as often in both the PDR and the non-PDR groups. Similarly, patterns of family life of a French cohort of young adults with T1D were comparable to the general population (Mellerio *et al.* 2015).

The age at onset of T1D has shifted towards younger children and especially those receiving T1D diagnosis early i.e. under five to seven years of age, are at an increased risk of developing cognitive deficits (Biessels *et al.* 2007, Desrocher & Rovet 2004, Gaudieri *et al.* 2008). Encouragingly, in the current population-based study, the young adults with early-onset of T1D were faring equally well in all measured aspects of social well-being compared to those with a later onset (Hannula *et al.* 2015). In addition, the prevalence of PDR was similar between the early- and later-onset subjects (Hannula *et al.* 2015).

Childhood onset T1D can add an extra challenge to an individual's maturation process and it also exposes all major life decisions to the potential influence of the chronic disease. However, the negative effect of T1D may seem greater to an observer than to the affected individual, especially in the absence of major complications. The onset of T1D particularly during early childhood enables efficient adaptation (Trento *et al.* 2014). In general, T1D does not pose a significant hindrance to normal social development as shown by the population-based cohort of the present study.

Although the results of the young adult cohort with a long disease duration are for the most part encouraging, T1D has the potential to mould a susceptible individual's course of life profoundly and impact also on future social development and well-being. The negative effect of advanced diabetic complications highlights the relevance of strict metabolic control and treatment adherence. Increased patient education may be beneficial in resolving adherence issues and gaining tools for better disease management. Sustaining healthy life and function from the time of diagnosis and minimizing the inconveniences

caused by the management of T1D, give patients the best possibility to pursue their desired life goals and to achieve a satisfying social position.

6.5 Strengths and limitations of the study

The population-based study design provided good population coverage and possessed the prerequisites for conducting a reliable evaluation of the paediatric and young adult cohorts. The cohorts were limited in size but represented selected populations.

There were good participation rates with the paediatric cohort since the examinations were incorporated into their regular three month follow-up visits to the hospital. The population-based setup ensured an accurate assessment of the current paediatric ophthalmic status in the hospital district. The results would be most likely similar throughout Finland since all centres adhere to the national Current care guidelines (Diabetes: Current care guideline 2013). Nonetheless, the present results revealed that the recent advances in the care of T1D have not exerted any positive influence on glycaemic control or ophthalmic status during almost two decades. Further evaluations will be required in the future to monitor the short- and long-term results of possible new treatment modalities in the paediatric population. Those results may help investigators to focus on aspects providing the greatest benefits to the patients.

The young adult cohort was contacted 18 years after their initial ophthalmic evaluation. Approximately two thirds of the cohort subjects participated in at least some part of the current study. Individuals more interested in personal health and possibly therefore in a better physical state may have been more prone to participate in this type of study. However, the available data gave no reason to assume that the rest of the cohort would have differed significantly in their values.

Advanced PDR and possibly other concurrent complications seem to negatively influence patients already during young adulthood. With the number of patients with T1D increasing and the age at onset declining, more patients are likely to experience the adverse impacts of this chronic disease. Monitoring the maturation and social development of these patients may help to detect disadvantaged subgroups or individuals and assist in targeting resources to those most in need. In the future, it would be interesting to evaluate the influence of cumulative glycaemic burden on the development of PDR. A larger population would also allow a more detailed assessment of the effects of other diabetic complications on patients' well-being.

7 Conclusions

1. The overall prevalence of DR and its risk factors, including glycaemic balance, had not changed significantly between the two population-based paediatric cohorts studied 18 years apart in 1989–1990 and 2007 in the catchment area of the Northern Ostrobothnia Hospital District. DR was detected in girls more frequently than in boys, with the difference having become more pronounced during the study period.
2. The young adult cohort with T1D since childhood had as good values of HRQoL as the age- and gender-matched population when PDR was not present. PDR was associated with a lower mean 15D score, with reductions noted in the dimensions assessing vision, usual activities, mobility and sexual activity.
3. The adult cohort with T1D since childhood had a high prevalence of DR with 94% of the evaluated subjects being affected. PDR had developed in one third of these young adults. No significant gender-related difference was detected in the prevalence or severity of DR.
4. The majority of the young adults with T1D since childhood had a social status comparable to the background population. However, PDR was associated with a lower secondary education level and a greater risk of being left without gainful work due to unemployment or pensioning.

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Appendix 15D questionnaire

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Ohje: Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka **parhaiten kuvaa nykyistä terveydentilaanne**. Menetelkää näin kaikkien kysymysten 1-15 kohdalla. Kustakin kysymyksestä rastietaan siis yksi vaihtoehto.

KYSYMYS 1. Liikuntakyky

- 1 () Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
- 2 () Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
- 3 () Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
- 4 () Pystyn kävelemään sisälläkin vain toisen avustamana.
- 5 () Olen täysin liikuntakyvytön ja vuoteenoma.

KYSYMYS 2. Näkö

- 1 () Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
- 2 () Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
- 3 () Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
- 4 () En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
- 5 () En näe kulkea oppaatta eli olen lähes tai täysin sokea.

KYSYMYS 3. Kuulo

- 1 () Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
- 2 () Kuulen normaalia puheääntä pienin vaikeuksin.
- 3 () Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
- 4 () Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
- 5 () Olen täysin kuuro.

KYSYMYS 4. Hengitys

- 1 () Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
- 2 () Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
- 3 () Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
- 4 () Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
- 5 () Minulla on hengenahdistusta lähes koko ajan, myös levossa.

KYSYMYS 5. Nukkuminen

- 1 () Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
- 2 () Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
- 3 () Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.
- 4 () Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
- 5 () Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

KYSYMYS 6. Syöminen

- 1 () Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
- 2 () Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
- 3 () Tarvitsen hieman toisen apua syömisessä.
- 4 () En pysty syömään itse lainkaan, vaan minua pitää syöttää.
- 5 () En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

KYSYMYS 7. Puhuminen

- 1 () Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.
- 2 () Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
- 3 () Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkkytäten.
- 4 () Muilla on vaikeuksia ymmärtää puhuttani.
- 5 () Pystyn ilmaisemaan itseäni vain elein.

KYSYMYS 8. Erytystoiminta

- 1 () Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
- 2 () Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa
- 3 () Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
- 4 () Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
- 5 () En hallitse lainkaan virtsaamista ja/tai ulostamista.

KYSYMYS 9. Tavanomaiset toiminnot

- 1 () Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
- 2 () Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
- 3 () Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
- 4 () Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
- 5 () En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

10. Henkinen toiminta

- 1 () Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
- 2 () Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti
- 3 () Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä
- 4 () Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä
- 5 () Olen koko ajan sekaisin ja vailla ajan tai paikan tajua

KYSYMYS 11. Vaivat ja oireet

- 1 () Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
- 2 () Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
- 3 () Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
- 4 () Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
- 5 () Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

KYSYMYS 12. Masentuneisuus

- 1 () En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
- 2 () Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
- 3 () Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
- 4 () Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
- 5 () Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

KYSYMYS 13. Ahdistuneisuus

- 1 () En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 2 () Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 3 () Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 4 () Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
- 5 () Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

KYSYMYS 14. Energisyys

- 1 () Tunnen itseni terveeksi ja elinvoimaiseksi.
- 2 () Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
- 3 () Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
- 4 () Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
- 5 () Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

KYSYMYS 15. Sukupuolielämä

- 1 () Terveystilani ei vaikeuta mitenkään sukupuolielämääni.
- 2 () Terveystilani vaikeuttaa hieman sukupuolielämääni.
- 3 () Terveystilani vaikeuttaa huomattavasti sukupuolielämääni.
- 4 () Terveystilani tekee sukupuolielämäni lähes mahdottomaksi.
- 5 () Terveystilani tekee sukupuolielämäni mahdottomaksi.

Original publications

- I Kubin M, Tossavainen P, Hannula V, Lahti S, Hautala N, Falck A (2011) Prevalence of retinopathy in Finnish children and adolescents with type 1 diabetes: a cross-sectional population-based retrospective study. *Arch Dis Child* 96(10): 963–8.
- II Hannula V, Hautala N, Sintonen H, Falck A (2014) Health-related quality of life – using the 15D instrument – of young adults with type 1 diabetes since childhood. Population-based Oulu cohort study of diabetic retinopathy. *Acta Ophthalmol* 92(3): 205–8.
- III Hautala N, Hannula V, Palosaari T, Ebeling T, Falck A (2014) Prevalence of diabetic retinopathy in young adults with type 1 diabetes since childhood. The Oulu cohort study of diabetic retinopathy. *Acta Ophthalmol* 92(8): 749–52.
- IV Hannula V, Hautala N, Tossavainen P, Falck A (2015) Social well-being of young adults with type 1 diabetes since childhood. The Oulu cohort study of diabetic retinopathy. *Scand J Public Health* 43(6): 623–8.

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1303. Tanner, Tarja (2015) Healthy young adults' oral health and associated factors : cross-sectional epidemiological study
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1306. Kujala, Tiia (2015) Acute otitis media in young children : randomized controlled trials of antimicrobial treatment, prevention and quality of life
1307. Kämppi, Antti (2015) Identifying dental restorative treatment need in healthy young adults at individual and population level
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1310. Valtokari, Maria (2015) Hoitoon pääsyn moniulotteisuus erikoissairaanhoidossa
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1312. Kallio-Pulkkinen, Soili (2015) Effect of display type and room illuminance in viewing digital dental radiography : display performance in panoramic and intraoral radiography
1313. Roivainen, Eka (2015) Validity in psychological measurement : an investigation of test norms
1314. Puhto, Ari-Pekka (2015) Prosthetic joint infections of the hip and knee : treatment and predictors of treatment outcomes
1315. Pentikäinen, Ilkka (2015) Distal chevron osteotomy for hallux valgus surgery : role of fixation and postoperative regimens in the long-term outcomes of distal chevron osteotomy – a randomised, controlled, two-by-two factorial trial of 100 patients
1316. Mikkonen, Paula (2015) Low back pain and associated factors in adolescence : a cohort study
1317. Hakalahti, Antti (2015) Efficacy and safety of radiofrequency catheter ablation in the treatment of atrial fibrillation

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