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End stage renal disease in type 1 diabetes- Time trends and risk factors

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Populärvetenskaplig sammanfattning

Sverige har en hög insjuknandefrekvens av typ 1 diabetes. Även i övriga delen av världen ser man en ökning av sjukdomen. Sedan 1977 har man i Sverige registrerat barn under 15 år som nyinsjuknat i typ 1 diabetes och man har sett en dubblering av antalet nya fall sedan registrets början. Det är känt sedan länge att en av de viktigaste riskfaktorerna för att utveckla sena komplikationer till diabetes, såsom njursvikt, är hur länge man har varit sjuk. Om insjuknandet sker tidigt i livet kan detta leda till att vi får unga patienter med allvarliga komplikationer. Det är därför viktigt att följa dessa patienter över tid för att se om risken förändras.

I den första studien ville vi studera tidstendenser i hur många personer i Sverige som utvecklat dialyskrävande njursvikt (ESRD) oavsett njursjukdom samt jämföra de två diabetessjukdomarna och övriga orsaker till njursvikt. Vi ville också jämföra vid vilken ålder de utvecklade ESRD. I denna studie visste vi inte hur länge de varit sjuka i sin diabetes eller när de insjuknade i diabetes. I studie 2 däremot ville vi titta närmare på de som utvecklat sin typ 1 diabetes när de var yngre. Hur såg deras risk för att utveckla njursvikt ut och hade risken ändrats över tid. Var det samma risk för båda könen? I denna studie var ålder när de insjuknande i typ 1 diabetes och hur länge de haft sjukdomen kända. I studie 3 studerade vi socioekonomiska faktorer på individ och föräldranivå och hur de påverkar risken att utveckla njursvikt. Vissa kända riskfaktorer för att utveckla ESRD kan inte påverkas, t.ex. kön och gener. En viktig riskfaktor som däremot kan påverkas är blodsockerkontrollen. Att sköta sin diabetes kräver en stor insats från patienten och det är dagligen flera övervägda beslut som ska fattas. Detta kräver en stor förförståelse kring sjukdomen från patienten men framförallt från föräldrarna till diabetesbarnen. Att vara socialt utsatt med dåligt skyddsnät och/eller ha en lägre utbildning ger en hög stress generellt men också kring att sköta sjukdomen. Sedan tidigare är det också känt att dessa sociala faktorer påverkar hälsa och dödlighet negativt på ett befolkningsplan. Målet med den fjärde studien var att titta på överlevnad hos patienter med ESRD på

grund av typ 1 diabetes och vad de dör av. Vi ville även analysera överlevnad i olika behandlingsalternativ och om val av behandling hade ändrats över tid.

För att kunna göra dessa studier använde vi oss av ett antal nationella register. I första studien användes enbart Svenskt Njurregister. I de övriga studierna var det Svenska barndiabetesregistret basen. Detta, samt för studie 2 även Nationella diabetesregistret och DISS, kopplades till njurregistret för att hitta de individer som utvecklat ESRD. I studie 3 kopplades data till SCBs databas LISA för att få fram socioekonomiska uppgifter på patienter och föräldrar.

Under den studerade tidsperioden har insjuknandet i ESRD legat på en stabil nivå i befolkningen samtidigt som den har sjunkit för ESRD orsakad av typ 1 diabetes. Detta trots att vi ser en ökning av typ 1 diabetes i befolkningen. Medelåldern vid debut av ESRD har dessutom ökat med mer än 3 år sedan mitten av 90-talet. Dessa förändringar ses inte för övriga patienter som fått ESRD och för typ 2 diabetes ser man en ökning i antalet nya fall. I alla grupperna var det fler män som fått ESRD.

Vi fann en fortsatt låg frekvens av nyinsjuknade i ESRD orsakad av typ 1 diabetes. Bland de som fått diabetes som barn eller unga vuxna (0-34 år) låg den på drygt 5 %, efter en maximal uppföljningstid på 38 år (median 23 år). Vi såg också en minskning i antal nyinsjuknande i ESRD i denna grupp över tid. Det fanns i vår studiepopulation ingen könsskillnad i risken att utveckla ESRD.

Den enskilt starkaste socioekonomiska riskfaktorn för att utveckla ESRD var barnets/patientens egen utbildningsnivå. Om man inte gått ut gymnasiet var risken att få njursvikt mer än 5 gånger större än om man gått färdigt gymnasiet. När vi undersökte riskerna på föräldranivå såg vi att båda föräldrarnas, men särskilt mammans, högst uppnådda utbildning också var en stark faktor. Vad gällde om någon i familjen fått socialbidrag vid något tillfälle kunde vi se att även det hade en negativ påverkan på barnets risk att utveckla ESRD.

Färre patienter utvecklar ESRD på grund av typ 1 diabetes kunde vi se i de övriga studierna men hur går det sedan? Det verkar som om patienter som utvecklat ESRD under senare tid överlever längre i behandling än de som insjuknade på 90- och början av 2000-talet. Bäst överlevnad sågs hos de som blivit njurtransplanterade vilket drygt hälften av patienterna i studien blev.

Slutsatsen är att i det stora hela är bilden positiv där färre patienter med typ 1 diabetes utvecklar terminal njursvikt. De utvecklar dessutom den senare i livet numera och lever längre med den. Större vikt behöver läggas på socioekonomiska faktorer vid omhändertagandet av dessa unga patienter och deras familjer. Trots ett väl utvecklat skyddsnät från samhället ser vi tydliga skillnader i risk beroende på hur förutsättningarna ser ut ekonomiskt och efter utbildningsnivå.

Abstract

Background and aims: Sweden has a high incidence of type 1 diabetes (T1D) and the incidence is increasing worldwide. The incidence is now twice as high as when the registration of childhood onset T1D in Sweden started in 1977. One of the major risk factors for developing late complications such as renal failure (ESRD) is duration of T1D. With a disease onset early in life this could lead to young patients with serious complications. It is therefore of interest to follow these patients to see how the risk for complications develops over time. In the first study, time trends in onset of ESRD due to diabetes (T1D and T2D) and other causes of kidney failure were studied as well as the age at onset of ESRD. To follow up on this, the aim of the second study was to analyse the cumulative incidence of ESRD and analyse possible time trends and gender differences in a younger diabetes population with known T1D duration. An earlier study had shown a low incidence of ESRD and now 8 more years of follow up could be added. Besides genetics, metabolic control is a factor with strong impact on the future risk of complications. The social environment of the child and adolescent with diabetes influence the understanding and management of the disease and hence the blood glucose control. Social vulnerability and/or low education imposes even more stress on the individual which could negatively influence disease management. The aim of the third study was therefore to study the impact of socio-economic status (SES) on the risk of developing ESRD in the young diabetes population. The aim of the fourth study was to analyse time trends in the treatment choices once the patients develop ESRD, the survival and cause of death in treatment and how it has developed over time.

Study population: In all studies, data from the Swedish Renal Register (SRR) were used. The data on the T1D patients with onset before the age of 15, used in studies II-IV, came from the Swedish Childhood Diabetes Register (SCDR). In study II we also retrieved data from the Swedish National Diabetes Register (NDR) and the Diabetes Incidence Study in Sweden (DISS). All registers have national coverage. The diabetes registers were linked to the SRR to

find the patients who had developed ESRD. In study III we used the linkage between the SCDR, the SRR and Longitudinal integration database for health insurance and labour market studies (LISA).

Results: Even though the incidence of ESRD in Sweden remained stable, the incidence of ESRD due to T1D decreased over the studied years, 1995-2010. We did not see a concurrent change for T2D. The age when the T1D patients developed ESRD had increased by 3 years and this was not seen in patients with other causes of ESRD. For patients in the SCDR the increase in age at onset of ESRD was almost 6 years. The cumulative incidence of ERSD in Sweden due to T1D is still low, 5.6% at a maximum follow up of 38 years (median 23). The incidence of ESRD is decreasing when comparing onset of T1D in the 1970´s and 80´s to onset in the 90´s, even when adjusting for T1D duration. Once the patients had developed ESRD, the survival in renal replacement therapy (RRT) had also improved over the years. The longest survival was seen after receiving a kidney transplant which more than 50% of the patients do.

When analysing social risk factors for development of ESRD we found that the educational level of both parents, but especially the mother´s, affected the child's risk of developing ESRD. The strongest association of education however was seen in the T1D patients own education. There was also an increased risk of developing ESRD if any or both of the parents had received income support.

Conclusion: The incidence of ESRD due to T1D is decreasing in Sweden and the age at onset of ESRD has increased by at least 3 years. There was a significant decrease in development of ESRD over time. The patients have a longer survival once in RRT today and many of them are transplanted, further improving their survival. Growing up in families with a lower SES increases the risk of later developing ESRD, a finding worthy of recognition in the clinical setting.

List of original papers

This thesis is based on the following articles and manuscripts which will be referred to in the text by their Roman numerals (I-IV). The published papers have been reprinted with the permission from the publishers.

I. Toppe C, Mollsten A, Schon S, Jonsson A, Dahlquist G. Renal replacement therapy due to type 1 diabetes; time trends during 1995-2010--a Swedish population based register study. J Diabetes Complications. 2014;28(2):152-5.

II. Toppe C, Mollsten A, Waernbaum I, Schön S, Gudbjörnsdottir S, Landin-Olsson M, Dahlquist G Decreasing cumulative incidence of end-stage renal disease in young patients with type 1 diabetes in Sweden. A 38 years prospective nationwide study. Diabetes Care 2018 Oct; dc181276; e-published ahead

III. Toppe C, Mollsten A, Schon S, Dahlquist G. Socio-economic factors influencing the development of end-stage renal disease in people with Type 1 diabetes – a longitudinal population study Diabetic Medicine, May 2017, Vol.34(5):676-682

IV. Toppe C, Mollsten A, Schon, S, Dahlquist G Improved survival in Renal Replacement Therapy for type 1 diabetes patients in Sweden- a national registry study. In manuscript

Abbreviations used in the thesis

CVD-cardiovascular disease

CVL-cerebrovascular lesion

DISS-Diabetes Incidence Study Sweden

DN-diabetic nephropathy

EDTA-European Dialysis and Transplantation Association register

ESRD-end stage renal disease

GFR-glomerular filtration rate

HbA1c-glucosylated haemoglobin

HD-haemodialysis

LISA- Longitudinal integration database for health insurance and labour market studies

NDR-National Diabetes Register

PD-peritoneal dialysis

RRT-Renal Replacement Therapy

SCDR-Swedish Childhood Diabetes Register

SRR-Swedish Renal Register

T1D-type 1 diabetes

T2D-type 2 diabetes

TX-kidney transplantation

Introduction

History of diabetes

Diabetes Mellitus is a disease mentioned as early as ancient times. The earliest known record is from 1552 BC, where an Egyptian physician named Hesy-Ra mentioned polyuria as a common symptom. A sweet taste of the urine in polyuric patients was also described from India in the medical script of Sushruta (600BC-500AD). The curiosity to taste the urine came from the fact that it attracted ants and flies.

The Greek physician Aretaeus of Cappadocia (120-180 AD) described the now well-known symptoms of polyuria, increased thirst and weight-loss very colourfully:

"Diabetes is a dreadful affliction, nor very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking, their mouths become parched and their bodies dry; their viscera seems scorched up, the patients are affected by nausea, restlessness and burning thirst, and within short time they expire"

He was also the one who gave the first part of the disease name, Diabetes, from the Greek word for "passing through". In the 17´th century the British physician Willis added the Latin word Mellitus meaning honey, referring to the sweet taste of the patients' urine.

The science of medicine developed fast in the 19th century. First, the Island of Langerhans was described in 1869 by Langerhan, a German medical student at the time, although their function was unclear. Lancereaux proposed the idea that the cause of diabetes could be found in the pancreas, an idea later confirmed when, in 1889 von Mering and Minkowski found that performing a pancreatectomi in dogs caused the development of diabetes. Lancereaux also described two variants of the disease, diebéte maigre (lean subjects) and diabéte gras (obese). When performing an autopsy on a diabetic patient, Barron found that the islets of

Langerhans were damaged. In 1910 Sharpey-Shafer suggested that patients with diabetes were missing a substance produced in the pancreas, and proposed the name insulin from the Latin word Insula. In 1921 Paulesco in Rumania first isolated insulin. In Toronto, Banting, a surgeon and Best, a medical student, supported by professor McLeod and the biochemist Collip were the first to isolate insulin and show that injecting the preparation gave the expected effect of lowering blood glucose levels in a diabetic dog. The first human injection of insulin was given on January 11th 1922, to a young boy, L. Thompson, 14 years of age. Banting and McLeod was given the Nobel Prize for their discovery in 1923. Since 1923 insulin has been commercially produced. The technical advances in insulin production, insulin delivery systems and at home devices for control of blood glucose have improved substantially over the years.

Diagnosis and definition of type 1 Diabetes

WHO classifies diabetes as a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which over time leads to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. Type 1 diabetes (T1D) is defined by the presence of markers of autoimmune destruction of the β-cell.

The diagnosis is easily suspected when the patient presents with the symptoms of rapid weight loss, polyuria and increased thirst. Normally the period of suspicion is short, only a few weeks of increasing distress. The first presentation can however be more dramatic in the form of ketoacidosis, a dangerous condition which, if not correctly suspected and treated, could lead to death. The rapid onset is more common in children and adolescence. The latest revision from ADA and WHO on the diagnostic criteria of diabetes states that a person with symptoms and a random venous plasma glucose level ≥11.1 mmol/l or a fasting plasma glucose of ≥7.0 mmol/l is considered as having diabetes. If these criteria are not met, an OGTT with a 2 hour glucose of ≥11.1 is also considered diagnostic (1, 2).

Type 1 diabetes aetiology

The aetiology of T1D is multifactorial with both environmental and genetic factors contributing to the development of the disease. The cause of the elevated glucose level in T1D is a reduced and eventually ceased production of insulin due to a T-cell driven destruction of insulin producing β-cells in the pancreatic islets (3). Up to 90 % of patients with type 1 diabetes are positive for one or more autoantibodies (4).

A strong association to T1D has been found in the human leukocyte antigen (HLA) locus, in particular the HLA DR3-DQ2 and DR4-DQ8. Combination of alleles at these loci of interest determines if the risk is high or low for developing T1D (5) and confers most of the genetic risk by affecting antigen presentation to T-cells (6, 7). Less than 10% of genetically susceptible individuals progress to clinical disease however. The concordance rate for developing T1D in monozygotic twins is only 13-30 % (8, 9).

This suggests that T1D incidence can´t be explained by genetics alone (10, 11). Migration studies have shown that moving from an area with a low incidence of T1D to a high incidence area increases the individual risk of developing T1D (12). Studies on environmental factors are plenty and not always conclusive. The autoimmune process starts long before clinical appearance of T1D and that could obscure the picture. The age at onset of T1D varies and the vulnerable time span for different environmental risk factors might variate. Several viruses have shown an association with the development of T1D but none of them are disease specific and must therefore be considered as one step in the pathway to developing T1D (13-15). Weak associations to dietary factors such as early introduction to cow´s milk, cereals and low vitamin D supplementation have been reported (3, 11, 16). There is a clear north-south gradient in incidence of autoimmune diseases as well as an obvious increase of autoimmune diseases over the last decades, both in the developed and the developing world (17). Formerly it was thought that the decrease in infections early in life was the culprit (“the hygiene hypothesis”) but now the theories lean

towards an altered exposure to microbes at young ages, rather than exposure to infections per se, failing to help the immune system develop correctly (18-20).

Other contributing factors also are at play. These are not considered as causative factors but rather responsible for accelerating the ongoing β-cell destruction. The “overload theory” states that children today are overexposed to calories, both intrauterine and during childhood. This leads to an accumulation of fat, a relative hyper-insulinism, insulin resistance and hence an extra stress on already damaged β-cells, leading to apoptosis of β-cells. This could be one reason why the disease often appears after or during periods with an increased demand of insulin, such as infection or periods of rapid growth, such as puberty (21-24). Fig. 1 shows a summary view on how T1D is thought to develop.

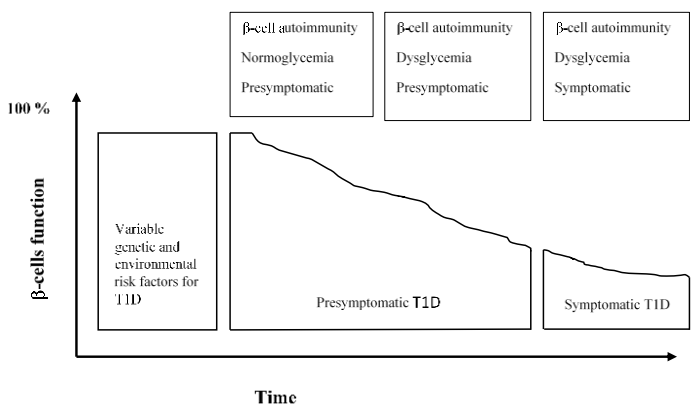

Fig. 1 How T1D is proposed to develop from asymptomatic □-cell destruction to fulminant disease. Adapted from Insel et al (25).

Background to thesis

Prevalence and incidence of type 1 diabetes

It is well known that the Nordic countries have a high incidence of T1D (26). In 1999, a report from several national reports found an annual increase of 3% worldwide of T1D. All included studies were done on T1D with onset before the age of 20, many before the age of 15. For Sweden the increase was smaller, 1.2 %, probably reflecting a good coverage in the register early on (27). A study from the Swedish childhood diabetes register (SCDR) in the early 80´s showed a yearly incidence of 23.6 per 100 000/year. It was also shown that the average difference in incidence between 1977-1980 and 1980-1983 was 3.5 per 100 000/year (28). A study from the EURODIAB group on T1D postulated that, compared to 2005, in 2020 the prevalence of T1D children would have risen by 70% and there would be a doubling in T1D incidence in children under the age of 5 years (29). The increasing incidence of 3.9% annually in that study was mainly driven by eastern and central Europe (29).The incidence of childhood onset T1D in Sweden is twice as high today as in the late 70´s, fig. 2.

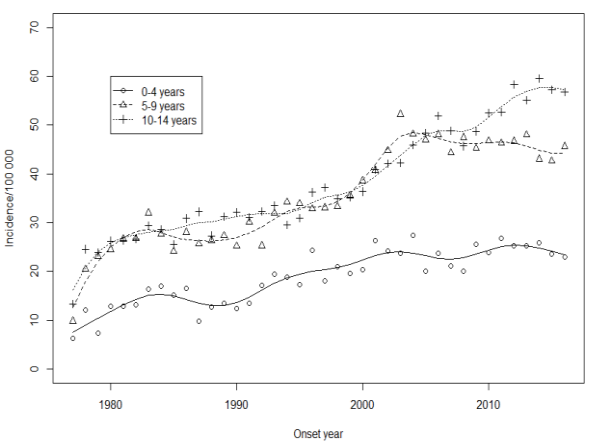

Fig. 2 The incidence of c hildhood onset T1D in Sweden from 1978 to 2016 according to age at onset of T1D. Unpublished data from the SCDR.

In Sweden all adult diabetes patients (18 years or older) are reported to the National Diabetes Register (NDR). The following data are collected from the annual report from 2016 (https://www.ndr.nu/pdfs/Arsrapport_NDR_2016.pdf). The prevalence of T1D was 0.5% of the Swedish population, which translates to 42 457 T1D patients having a registration that year. The mean age of the patients was 46.4 years and the mean T1D duration 24 years. Of the incident cases 55% were males and 403 incident cases were registered, giving an incident rate of 50.3 per million person years. The mean age of the incident cases was 35.6 years. The NDR has since 2000 included the SweDiabKids Register on their website. This register includes patients 0-17 years of age. In 2016 they reported 807 new patients with T1D onset. This corresponds to an incident rate of 389 per million person years. 59.2 % were boys. There are approximately 7000 children active in the register in 2016, giving a prevalence of 12.7% among people under the age of 18.

The kidney and the development of diabetic nephropathy (DN)

The normal kidney and glomeruli

The kidney is responsible for removing toxic substances from the blood. It also keeps pH stable, water and salt balance tightly regulated as well as maintaining blood pressure. The functional part of the kidney is called nephrons. In a young healthy person the kidney contains approximately 1 million nephrons. The nephron consists of the Bowman Capsule, which surrounds the glomeruli capillaries, and the tubule system with leads the primary urine away from the glomeruli, fig 3. The glomeruli capillaries are supplied from the a. renalis, a. interlobaris, a. arcuate, a. interlobularis and the afferent arteriola. The glomeruli is drained by the efferent arteriola which branches out to a peritubular capillary network and then eventually to the v. renalis. The afferent arteriole is wider in diameter than the efferent, which evokes a pressure gradient over the glomeruli. In a healthy young individual 1.2 litres of blood flows through the kidney every minute, about 25% of the cardiac output. This means that the renal plasma flow is 0.65 L/minute. The normal glomerular filtration rate (GFR) is 125 ml/min giving a filtration fraction of about 20%. What determines the amount of glomerular ultra-filtrate is the pressure gradient over the glomerular filtration barrier. The latter consists of the endothelial cells of the capillaries, the visceral cells in the Bowman capsule-the podocytes and the basal membrane layer (30).

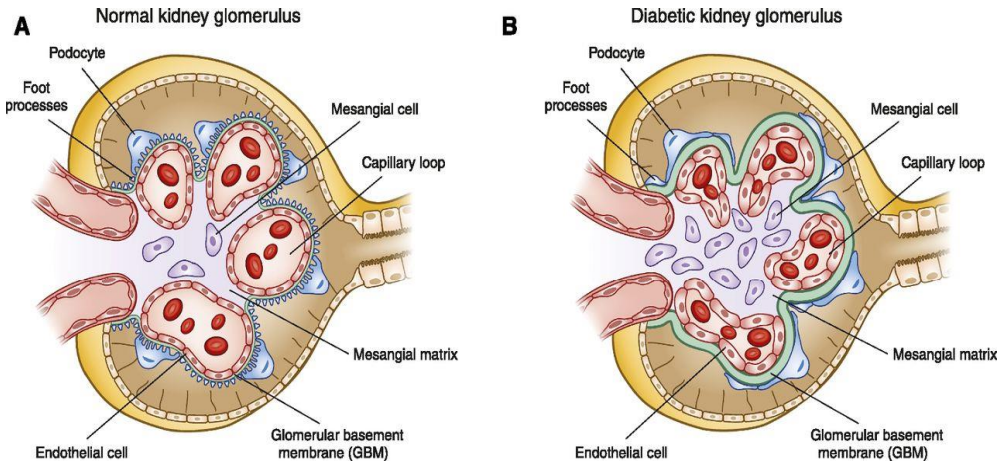

Fig. 3 The morphology of a normal glomeruli (A) and its diabetic counterpart (B). Adapted from Alicic (31).

The morphology of diabetes nephropathy (DN)

Three important structural changes have been described in DN; a thickening of the glomerular basal membrane, an expansion of the mesangial matrix and glomerular sclerosis (32-34), see also fig 3. The expansion of mesangial matrix is due both to an increased production and a decreased degradation of extracellular components. This leads to an increasing size of the mesangial area and the relationship in size between the mesangial area and the total glomerular volume is a histological measure of the severity of the nephropathy. This histological picture was first described by Kimmelstiel and Wilson in T2D and is known as the Kimmelstiel-Wilson nodulae (35). In the basal membrane, changes occur in all four layers: the glycokalyx, the fenestrated capillary endothelial, the basal membrane and the podocytes. Scanning electron microscopy of the basal membrane has shown that at late stages of diabetic nephropathy the foot processes of the podocytes are nearly completely lost and the basal membrane transformed (36). The loss of foot processes, the change in pressure gradient over the basal membrane and a reduction in negative charges over the membrane

is thought to lead to a progressive leakage of albumin. A compensatory hypertrophy of the glomeruli is mediated through growth factors delaying the onset of decreased GFR. At the same time, this exacerbates the effect on the mesangial expansion leading to occlusion and sclerolisation of the vessels. Evidence that receptors in the Renin angiotensin II aldosterone system (RAAS) exists on all structures in the glomeruli as well as a local synthesis pathway of Angiotensin II highlight the importance of this system in the pathogenesis of DN (37). Morphological changes in the glomeruli can be seen even before the appearance of albuminuria (38-40) and the decline in renal function precedes micro albuminuria (41).

The development of diabetic nephropathy

At the onset of T1D the kidney size is often increased and a period of hyper filtration occurs. The filtration normally reverts to normal or near normal with the start of insulin (42). Already when detectable levels of albuminuria occur, advanced structural changes in the glomeruli can be seen (43). Studies have shown that it is not necessarily a progressive disease, patients can for example go back and forth between normo- and microalbuminuria (44, 45). Once persistent micro or macro albuminuria were present, the rate of yearly decline in GFR was 1.8 and 5.7% respectively. But even macro albuminuria have been shown to be able to be reversed (44) or maintained and not always proceed to ESRD (46). In table 1 the different stages of kidney disease, CKD 1-5, is displayed and their relation to albuminuria level.

Prognosis of CKD by GFR and albuminuria categories			Albuminuria level		
			Normal to mildly increased	Microalbuminuria Moderately increased	Macro albuminuria Severely increased
Stage		GFR	<30mg/g <3mg/mmol	30-300mg/g 3-30mg/mmol	>300mg/g >30mg/mmol
1	Normal or high	>90			
2	Mildly decreased	60-89			
3a	Mildly to moderately decreased	45-59			
3b	Moderately to severely decreased	30-44			
4	Severely decreased	15-29			
5	Kidney failure	<15			

Table 1 The CKD stages according to KDIGO. Colours mark risk for developing cardiovascular disease or progressive kidney disease going from low=green to high=red. As albuminuria increases so does to the risk for progressive kidney disease and cardiovascular disease. Adapted from (47).

In some patients with longstanding T1D and retinopathy and/or hypertension, a quite advanced DN can be found even without micro albuminuria but with a reduction in GFR (38). There have been many studies confirming data that 10-30% of the T1D population progress to micro- or macro albuminuria within 10-15 years (48-52) and that as many as 75% of patients with proteinuria will progress to ESRD in another 10 years (48).

Risk factors for End stage renal disease

Genes

As is the case in many diseases, large studies on genes and GWAS (Genome wide association study) have been conducted in order to find the cause of DN. None of them have found "the gene" but rather genes (or more specifically alleles) that in certain circumstances, such as a hyperglycaemia state, increase the risk of developing DN (53-58). The fact that genes are important risk factors is apparent since it has been shown that a family history of cardiovascular disease or hypertension increases the risk for the T1D child to develop DN (59-61). It has also been shown that the metabolic control of T1D (i.e. HbA1c level) could have a genetic component (62).

Hormones

Male gender seems to be associated with a more rapid progression of chronic kidney disease in the general population (63, 64). Conflicting results are at hand when it comes to T1D and male preponderance. For T1D it seems that it could be an imbalance in the sex hormones that develops with diabetes that exert the increased risk. Both elevated testosterone levels and reduced oestrogen levels have been reported for T1D females and the opposite for males (65-67). Age at onset seems to affect the gender factor, onset of T1D in adolescence are unfavourable to both genders (68-70). With later onset of T1D the risk diverges between no differences (71) or a negative correlation to males (68, 69). Growth hormones and IGF-1 levels have been shown to affect the risk of developing ESRD (72, 73). Both levels of GH and IGF-1 have been shown to be altered in poorly controlled T1D (73). Low levels of IGF-1 and higher levels of androgens are related to a higher risk of micro albuminuria during puberty, especially for females (74).

Blood glucose

A much cited report favouring a strict metabolic control in terms of diabetes complications is the UKPDS (United Kingdom prospective diabetes study) on T2D (75) released in the 1990´s. The relationship between lower HbA1c and fewer complications was also described in the DCCT (Diabetes control and complications trial), the largest prospective study on T1D (76-78). Both the DCCT, in its follow up arm EDIC, and the UKPDS study also showed a sustained effect of the initial improved glucose levels. Even after many years of equal HbA1c levels in both the control and the intervention group, a difference in risk was seen, referred to as metabolic memory or legacy effect (79, 80). Studies from Sweden have shown that the metabolic control in the first year (81) or years (82) had an impact on later risk of developing complications. This was mainly driven by a sustained unfavourable control and unhealthier lifestyle in adulthood (81). However already in 1985 Krolewski et al had shown an association between metabolic control and development of DN (48) and since then many studies have confirmed metabolic control as a risk factor for DN (50, 52, 81-84). Elevated glucose levels leads to increased amounts of advanced glycation end products (AGEs), which are proteins or lipids that are glycated. AGEs induce structural and functional tissue damage. They also interact with receptors which activate and stimulate transcription factors, vasoactive hormones and cytokines and activate macrophages. Intracellularly, hyperglycaemia leads to an accumulation of fructose and sorbitol. Sorbitol is toxic and provokes cellular swelling, oxidative stress and eventually apoptosis. The hyperglycaemia also leads to changes in intracellular signalling pathways which ultimately leads to fibrosis (85, 86).

Blood pressure and RAAS

In 1998 results from the UKPDS showed a beneficial effect of lower blood pressure on micro- and macro vascular complications regardless which medication was used (87). In the IDNT (Irbesartan Diabetic nephropathy study) it was suggested that a

systolic blood pressure (BP) <130 was beneficial for the kidney but a BP <120 increased the all-cause mortality (88). The effect of lowering BP in this study was seen independent from the use of RAAS blockade. The current Swedish guidelines advocate a BP <140/85 in all T1D patients and all BP lowering drugs are equally recommended. If proteinuria is present, a BP<130 is recommended and here AII blockers or ACE-inhibitors are the recommended treatment choice (89). The rationale behind this is that several studies have shown an additive and BP independent effect of RAAS blockade on the risk for progressive kidney injury in micro and macro albuminuric patients (86, 88, 90-94). Early initiation of AII blockers did not show an effect on glomerular changes in normotensive normo albuminuric patients in kidney biopsies (95) or on albumin-to-creatinine excretion ratio in adolescents at high risk of progression to microalbuminuria (96). An additive effect of AII blockers to ACE inhibitors has been found (92) but discouraging results on dual RAAS blockade have also been reported with regard to the kidney with positive effect on the proteinuria but a higher incidence of acute kidney failure, hyperkalaemia and no protection against ESRD (97, 98). Studies have tried to determine which patients would benefit most from RAAS blockade. Certain ACE polymorphisms clearly are related to risk of developing ESRD (99) but also the efficacy of treatment (100). Since RAAS blockade has shown beneficial results in the T1D population with hypertension and/or albuminuria, with low adverse effects, it should be natural to consider it first choice when initiating treatment. Fig. 4 shows a summary view on how different factors influence the development of DN.

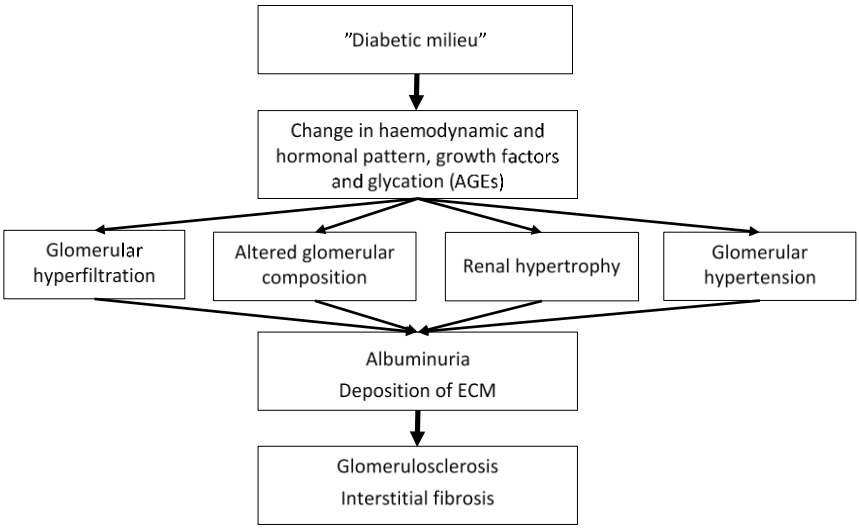

Fig. 4 A summary of the proposed pathophysiological pathway to DN. ECM= extracellular matrix, AGE advanced glycation end product. Adapted from Umanath et al (86).

Lipids

Patients with T1D and no DN normally have normal or elevated HDL. The opposite picture is seen in patients with DN where elevated levels of LDL, VLDL, triglycerides and a lower level of HLD are found (101). Dyslipidaemia has been described to increase the risk of developing DN, with various lipid components being more important at different stages (102-105). Metabolic control has also shown a relationship with levels of lipids (106, 107). A study in adolescents with albumin excretion rate in the high normal range showed no benefit with statin treatment on GFR or markers of cardiovascular risk despite the anticipated reduction in lipid levels (96). Perhaps the benefit from lowering lipids is mainly to be found in the reduction in macro vascular complications, where the effect has been extensively described (108-110). After manifest ESRD the effect of statins on risk of CVD is not as pronounced (111).

Socioeconomy

The socioeconomic status (SES) can affect a person's health in many ways. It could simply be not affording medications needed. But it can also affect health in more subtle ways. T1D treatment is a challenging one. It has been shown that T1D children have a higher mean HbA1c when the mother has lower education but also that the marital status of parents affect the metabolic control (112-114). A higher rate of Emergency Room visits for acute T1D complications at (115) or after (116) the diagnosis has shown to be connected with low SES. An association between parental and patients´ SES and mortality (117-120) and later complications to T1D (121, 122) has been described. An exposure to low SES in childhood tends to affect the health of the child also in adulthood, regardless of the child´s own SES level (123). A Swedish study showed that a prestigious job gave a healthy start and a slower deterioration in health. At the same time morbidity at onset of working life affects occupational mobility and income (124). In the T1D population a relation between high education, good metabolic control and low risk of complications have been shown. In the same study a relation between low education and an unhealthy life style with tobacco smoking and a sedentary life was also found (125).

Known general risk factors for the development of ESRD are obesity (126-129) and smoking (130-132). Both of these factors are more prevalent in individuals with lower SES (122, 133-136). Studies have also shown a relation between SES and risk of developing all cause ESRD even after adjustment for smoking, BMI and age. It seems that SES in itself can be an independent risk factor for developing ESRD (137).

Prevalence and incidence of End stage renal disease

The Swedish Renal Register (SRR) reported a prevalence of 9693 patients in renal replacement therapy (RRT) in 2017. The cause of ESRD was diabetes in 18% (both T1D and T2D). ESRD was more common in males, 66 %. There were 1180 incident cases of ESRD, or 118 per million person years. (Data from the SRR website, yearly report 2017). There have been a rather stable incidence of ESRD in Sweden for many years now and corresponds well with an earlier report (138). For T1D patients the incidence is decreasing from 119 new patients a year in the beginning of the 90´s (35% of diabetes cases) and now down to 83 a year (21% of new diabetes cases). For T2D there is an increasing incidence. Diabetes is still the most prevalent diagnosis. Earlier reports from the European Dialysis and Transplant Association Register (EDTA) showed that in the 1960-80´s, diabetes was an uncommon diagnosis in those accepted for RRT, less than 2% before 1975. The proportion of patients with diabetes rose steeply however and was on average 11% in Europe in 1985. Back then the majority of diabetes patients considered for RRT had T1D (139). In 2005 new results were issued from the European Renal Association (ERA) and EDTA. They found that in the last decade prior to the study there had been a rapid increase in T2D patients entering RRT but also an increase in T1D (140).

From early studies on ESRD and T1D from the Steno Centre in Denmark a cumulative incidence of 45% after 40 years was reported (49). More recent studies show more encouraging results. A cumulative incidence of ESRD of 3.3% after up to 30 years of diabetes duration was reported in a study from the Swedish Childhood Diabetes Register group (68). From Norway a cumulative incidence of 2.9 % was reported after 30 years of T1D duration in a population with onset before the age of 15 (70), and 4.8 % when onset was between 15 and 29 years (71). Finland, also with a well-developed national register on diabetes, reported a cumulative incidence of 7.8% after 30 years of diabetes duration (141) but their population was older (T1D onset in the 50´s and 60´s included). Studies from the United States have reported

variable results, both much higher incidences of around 20% after 30 years of T1D (142, 143) but also very favourable numbers around 2-3% from dedicated centres (144).

Renal replacement therapy

History

Already in 1913 Abel, Rowntree and Turner constructed a dialysis unit with a colloid membrane that they used in animal trials. The first human dialysis session was performed in 1925 by Haas, using the Abel-apparatus. He stated that "*it could be shown for the first time that blood purification by dialysis can be carried out in humans without exposing the patient to injury*". However, the attitude at the time was "*removing urine toxins provided no long-term benefit because it did not reverse the shrinking process of the kidney*". Therefore it was not until the 1940´s that dialysis was more commonly used, with names such as Kolf, Alwall and Kiil being renowned for the technical development. Still, it was considered against nature to use in a long term situation. By the end of the 50´s the dialysis shunt was introduced and recurrent treatment as we know it today was made possible and haemodialysis was born.

In the 1920´s the idea of peritoneal dialysis was first suggested by Ganter and Putnam but it was not put into use until the 1950´s as a treatment of acute kidney failure. Continuous peritoneal dialysis was introduced in the 1970´s.

The first successful transplantation of a kidney was performed in 1954 by J. Murray. The transplanted kidney came from the patient´s identical twin and the patient lived for twelve years after the surgery (30).

Haemodialysis (HD)

HD is the oldest form of renal replacement therapy and since the 1960´s an established treatment of chronic renal failure in Sweden. It is also the most common treatment for ESRD in Sweden according to the SRR yearly report from 2017. The technology, membranes and solutions used have developed over time. Two different chemical principles are used, diffusion and ultrafiltration. Diffusions means that soluble molecules travel across a semipermeable membrane to reach osmotic equilibrium. This is a passive action driven by the concentration gradient over the membrane. Ultrafiltration on the other hand is driven by the pressure gradient over the membrane. This is created by the higher mean blood pressure on the "blood side" and lower pressure on the "filtrate side". The net flow of water towards the low pressure side also permits a co-transport of soluble molecules, regardless of concentration gradient. The membranes vary in function and specificity, for example in size of the pores allowing molecules to pass. This allows the dialysis to be more specific to the patients` needs. The molecules and metabolites removed from the blood stream are, among others, urea, creatinine, B2-microglobulin and phosphatase.

In a normal dialysis session 250-400ml blood/min is required and the session itself takes about 2-3 hours, 3-4 times a week. Today it is possible to have HD at home which offers more freedom (30).

Peritoneal dialysis (PD)

PD is a form of dialysis which is often preferred when the patient has a remaining (albeit not sufficient) kidney function. It also takes advantage of the chemical phenomena of osmosis. Over the surface of the peritoneum an osmotic gradient is constructed through the delivering of a high osmotic pressure in the dialysate. The exchange of solubles are mainly through the capillaries of the peritoneum and the capillary walls are the main barrier. There are three sites were the exchange takes place; via specific aquaporines only transporting molecules smaller than or equal in size to water,

pores between the cells of the capillary walls and via special pores for larger molecules, only functioning passively and pressure dependent. The peritoneal space is filled and drained by hydrostatic pressure through a Tenckoff catheter. The opportunity to self-manage the treatment offers a better quality of life (30).

Kidney transplantation (TX)

TX is the third alternative to replace the non-functioning kidney. For the right patient it is the best treatment for ESRD and is compatible with continuing on the labour market (145). Contraindications are basically comorbidities such as uncured malignancy, chronic respiratory insufficiency, advanced heart failure, addiction to drugs or mental disorders rendering it hard for the patient to adhere to the adjuvant immunosuppressive treatment. Older age is a relative contraindication. The best results regarding survival of transplant is seen when the donor is a HLA matched sibling. Two donor sources exist, living donor - often a relative, or donation from a newly deceased, often someone killed in an accident. Kidneys donated from persons aged 0-80 years are accepted in Sweden. A living donor is considered preferable due to better survival of the transplant (30).

Survival in renal replacement therapy

In the 70´s a survival time of less than 3 years after the onset of ESRD due to T1D was reported. With advanced ESRD it was only 7 months (146). The survival time has improved over the years and later studies have shown a survival time of 4-8 years in the T1D population (147, 148). There have also been positive time trends with longer survival time in those starting RRT in more recent years (148, 149). A large European register study showed an improved 5-year risk of death in the ESRD population as a whole between a more recent cohort and an earlier (150). The improvement in survival in the study was predominantly driven by a reduction in cardiovascular disease which have been found in other studies as well (151). There have been an increase in patients being transplanted, the treatment modality with the best survival

(150). The limiting factor is normally availability to suitable organs. An improvement in survival of kidneys from deceased and marginal donors has been seen (150) and this can facilitate finding suitable donors. Greater benefits in survival rate with TX in younger patients and patients with diabetes has been reported (152).

Aims and objectives

DN, and its final stage ESRD, has been shown to be related to a high mortality (49, 71, 146) and higher risk of developing cardiovascular disease (CVD) and cerebrovascular disease (CVL) as well as death from these causes (139, 151, 153, 154). To continue to follow the development of and survival in ESRD is therefore important.

The overall objective of this thesis was to describe time trends in development of and survival in ESRD due to T1D and to increase the knowledge on how a number of risk factors influence the development of ESRD.

More specifically the aims were:

- To investigate the overall incidence of ESRD in Sweden between 1995 and 2010 and specifically look at T1D and time trends. (Paper I)

- To follow up on the cumulative incidence of ESRD in a population with T1D onset before the age of 35 and assess time trends. (Paper II)

- To evaluate how the socioeconomic environment experienced during childhood and early adulthood influence the risk of later developing ESRD. (Paper III)

- To analyse time trends in survival in RRT and also study trends in choice of treatment modality over time. (Paper IV)

Study population

The Swedish Renal Register (SRR)

The SRR was used in all four studies. It is a merge of the Swedish Register for Active treatment of Uraemia (SRAU) which started in 1991, the Swedish Dialysis Database (SDDB) started in 2002 and regional kidney failure registers in the county of Stockholm and Västra Götaland. Data that had formerly been reported to EDTA were included in the database after thorough validation. From 1991 the SRR has a prospective prevalence approach.

All patients with ESRD starting active RRT, such as dialysis or kidney transplantation, are reported to the SRR. Every patient is asked to give their informed consent before registration and very few patients decline to participate.

Reported data on patients include, besides age and gender, original kidney disease, treatment modality, comorbidity regarding diabetes mellitus, hypertension, cardio- and cerebrovascular diseases, malignancy and, in the case of transplantation, also the origin of the donor. At least once yearly, data from the SRR are linked to the Cause of death register, maintained by the National Board of Health and Welfare, also updated in a yearly basis.

At present all 65 dialysis and transplantation units reports to the SRR. A validation was done in 2004 showing a coverage of >95% (138).

The Swedish Childhood Diabetes Register (SCDR)

To enable us to answer the research questions in Papers II-IV, the SCDR was used. Patients with a newly diagnosed T1D are normally initially treated at a paediatric clinic. The paediatric clinics then report newly diagnosed cases to the SCDR, after informed consent of the parents. Data reported are the patients unique PIN (personal identification number), birth date and date of diagnosis. Date of diagnosis is set at first injection of insulin.

The SCDR was started July 1, 1977 as a prospective incidence register on childhood onset (0-14 years) T1D. Internal and external validation of the register have showed nearly 100% coverage (155). Due to the normally abrupt onset of T1D in this age group and that other forms of diabetes often present with a clinically different picture and are scarce, misclassification is rare. To ensure the quality of data, the SCDR has since 2003 introduced a continuous validation alliance with the Swedish Quality Assessment Register, which covers age-groups 0–18 years. Similar methods of collecting and verifying data have been used from the start of the SCDR until 2010. Since then, the incident cases come from reports from the Swedish National Drug Register, kept by the National Board of Health and Welfare since 2005. Data retrieved, besides PIN, is date of first prescription of insulin which is then considered as date of T1D onset.

The SCDR ensures a reliable source of data, now with more than 18000 cases of T1D, making it possible to conduct studies on this rather large T1D population with a follow up of up to 40 years.

Swedish National Diabetes Register (NDR)

In Paper II, the aim was to study the cumulative incidence of ESRD in patients with diabetes onset until the age of 34. An association with age at onset and gender has previously been shown, with early onset of TD being more favourable regarding risk of developing ESRD. To be able to study the incidence of ESRD in patients with T1D onset after the age of 15 years, a national register with good coverage in the desired age group (15-34 years) was required. The NDR is maintained by the Swedish Society for Diabetology. It was launched in 1996 with the intent to deliver up-to-date information about changes in treatment of diabetes and/or its complications and development in treatment and complication rates. It is a prospective prevalence register. All causes of diabetes are registered. Patients are entered at or after the age of 18 years, after informed consent. A validation study in 2014 showed that 91 % of the patients are correctly classified as having T1D. The ascertainment in 2007-2008 was only 59% (156). In the latest yearly report (2016) they

state a coverage of 91%, this however includes all diabetes diagnosis. T1D patients normally attend hospital based diabetes teams and are therefore more likely to be reported. Since it is a prevalence register patients have the opportunity to be reported afterwards, still with correct data regarding year of onset. It is possible that the lower coverage in the first years of the register affects our results. Patients who could have or did develop ESRD might not have been entered in the register thus affecting the results. However we consider it equally likely that persons who would not have developed ESRD are missing in the register.

Diabetes Incidence Study Sweden (DISS)

As mentioned, the aim in Paper II was to analyse the cumulative incidence of ESRD in patients with onset of T1D between the ages of 0-34 years. Already linked to the SCDR database was incident cases from the DISS study. They were used to complete data from the NDR with the intent not to lose patients with T1D onset between 15 and 18 years. The DISS records incident diabetes cases (T1D, T2 and unclassified) in the age group between 15-34 years prospectively, since 1st January 1983. Classification of diabetes in DISS was initially made according to the WHO classification but changed to the ADA classification criteria in 1992. In a validation study, using diabetes related antibodies and C-peptide levels, less than 10 percent of the T1D diabetes patients were misclassified (157). Depending on the source of ascertainment the register has shown 82% and 91% of completeness, with no significant gender difference (158). However in a study from 2014, the ascertainment in 2005-2007 was only 25 % (156) , which strengthens the decision not to redo the linking to the register after 2007.

Statistics Sweden and the LISA database

In Paper III the aim was to analyse associations between socioeconomic status of both the parents and the adult patients and the T1D patient's risk of developing ESRD. Data on parents and adult patients regarding highest achieved education and need of income support was retrieved from the LISA database.

Statistics Sweden has as its main focus to provide the Swedish authorities and researchers in Sweden with up to date and accurate statistics regarding population. It has its origin in the Swedish Tabellverket, started in 1749, and is one of the oldest record of a nation´s inhabitants in the world. It has been available online since 1995 (data from the Statistics Sweden website). In 1990 the Longitudinal integration database for health insurance and labour market studies (LISA) started and is maintained by Statistics Sweden. The database integrates existing data from the labour market and the educational and social sectors. All socioeconomic data on an individual as well as on a household level are registered. LISA accumulates data on demographics, education, employment and income, including that from salaries and various benefits (for example sick leave compensation, unemployment benefits, pensions and income support). Data is updated yearly. All Swedish citizens 16 years of age or older as of December 31 are included. For Paper III, data on highest achieved educational level and need of income support was retrieved from LISA.

Ethical consideration

All studies were approved by the regional research ethics committee in Umeå, according to the Swedish law on research ethics and in line with the principles of the Helsinki Declaration and the European convention on human rights and biomedicine.

The nationwide diabetes incidence registers (SCDR and DISS) were approved by the Swedish Data Inspection Board and the regional research ethics committees (Karolinska Institutet, Stockholm and Umeå University, respectively). Parents or patients gave individual informed consent to be registered in the incidence registers.

The study in Paper III was also approved by the ethics committees at the National board of Health and Welfare and Statistics Sweden respectively. Linkage between national register data was performed at Statistics Sweden and only coded data were delivered to the

researchers. According to current Swedish regulation, the use of national register data does not require informed consent.

Statistical methods

For the statistical analyses SPSS for Windows was used. To assess distribution patterns between groups in categorical variables the Chi square-test was used. The Oneway ANOVA was used in Paper I to analyse differences in mean values (age at onset) between groups. To try to reduce the faulty effect that can be imposed on a result after multiple testing in the ANOVA, Bonferroni adjustments were made. Cox regression was used to analyse variables influence on outcome of interest, ESRD (Paper II-III) or death (Paper IV). Since sex, age at onset and duration of T1D have been shown to affect the risk for complications we also adjusted for these variables in the Cox regressions where applicable. In Paper IV we adjusted for age at onset of RRT instead of age at onset of T1D. Kaplan Meyer analyses with log rank testing was used to analyse survival data. The Lifetable analysis was used to calculate cumulative incidences. In Paper II, the statistical software "R" (R-foundation for statistical computing, http://R-project.org/) was used for the analyses on death as competing risk, which supplements the data from Cox regression and Life table analyses. The method adjusts for the fact that death might occur prior to the event of interest (onset of ESRD) in susceptible individuals and hence provides a more accurate estimation of the risk (159). P-values of <0.05 was considered significant.

Major findings

Time trends in ESRD due to diabetes and other causes (Paper I)

In Paper I the aim was to analyse the incidence of ESRD due to T1D, T2D and other causes but also to look for time trends in incidence and age at onset of RRT. The other causes group included all non-diabetic causes of ESRD. The study population consisted of 17389 incident cases between 1995 and 2010. More than half of the patients were men, 64.8% (11252). This male/female ratio was somewhat lower for T1D patients (62.5 %). Among the cases, 10.5% (1833) and 14.1% (2457) had T1D and T2D respectively registered as cause of ESRD. The mean age at onset of RRT was 63.3 years. For T1D patients it was 58.4 years.

Time trends in incidence and treatment modality

The incidence of RRT remained stable in Sweden throughout the study period, about 119 cases per million persons and year or around 1078 new patients starting RRT each year. For patients with T1D, the incidence of ESRD is going down, this is not seen for T2D, fig. 5.

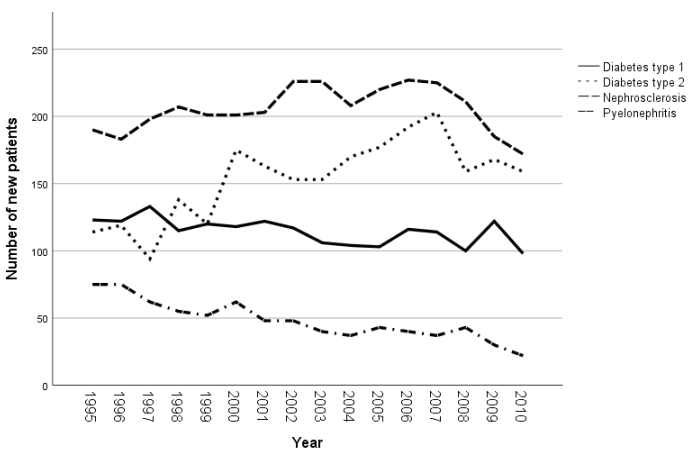

Fig. 5 The number of new patients receiving RRT in Sweden as a function of the year of onset of RRT and cause of ESRD.

There was no significant change in TX frequency over time in any group. PD was first treatment choice for 45 % of T1D and it remained stable over time. For ESRD due to T2D and other causes PD increased over time, from around 25% to over 30%.

Time trends in age at onset of RRT and gender

Over time the age at onset of RRT increased by 3.3 years in the T1D population ($p<0.01$). The same increase in age at onset of RRT was not seen for T2D or the other causes group. Women started RRT approximately 1.4 years earlier than men in the T1D population ($p<0.05$). In T2D, women were 1-2 years older than the men at onset of RRT, not significantly though. The right shift in age at onset and peak incidence of ESRD among T1D patients with later calendar onset is shown in fig. 6, the peak in the latest cohort is at around 70 years of age.

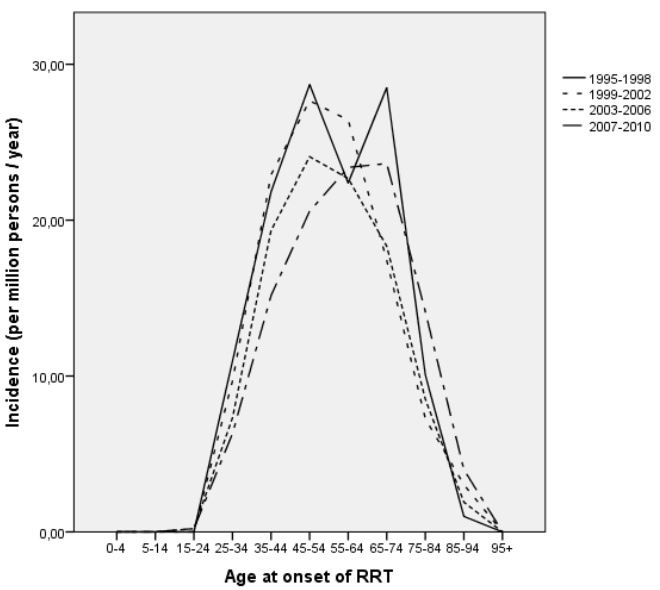

Fig. 6 Incidence of RRT per million persons, due to type 1diabetes in different time periods, as a function of age at start of RRT.

Cumulative incidence of ESRD in a population with T1D onset at 0-34 years (Paper II)

In this study we wanted to analyse incidence trends in ESRD over time and to follow up on a former study from the SCDR on cumulative incidence of ESRD. A total of 18760 patients were analysed from three national diabetes registers: 10322 from the SCDR (T1D onset <15years), 7630 from NDR (T1D onset 18-34 years) and 808 from DISS (T1D onset 15-34 years). The maximum T1D duration was 38.1 years for patients in the SCDR and 32.6 years for the NDR and the DISS. In the study population, 317 patients had developed ESRD due to T1D after a median duration of 22.9 years.

Incidence rate and cumulative incidence

The cumulative incidence of ESRD was 5.6 % after 38 years of T1D, 5.9% and 5.3 % for males and females respectively.

As we wanted to search for time trends in the incidence of ESRD we compared onset of T1D in different time periods and found that the incidence had decreased with time, even after adjusting for age at follow up and sex. The risk was 3.5 and 2.6 times higher when onset was in 1977-1984 and 1985-1990 compared to 1991-2001 (Fig 1 Paper II).

The incidence rate of ESRD increased with diabetes duration. For patients with diabetes onset at 0-9 and 10-19 years of age there was an increase in incidence up to 36 years of duration, at longer durations the number of cases is small and data more insecure, but a decrease is seen. With diabetes onset at 20-34 years of age the incidence rate increases until 25 years of diabetes duration and then a decrease can be observed, fig. 7.

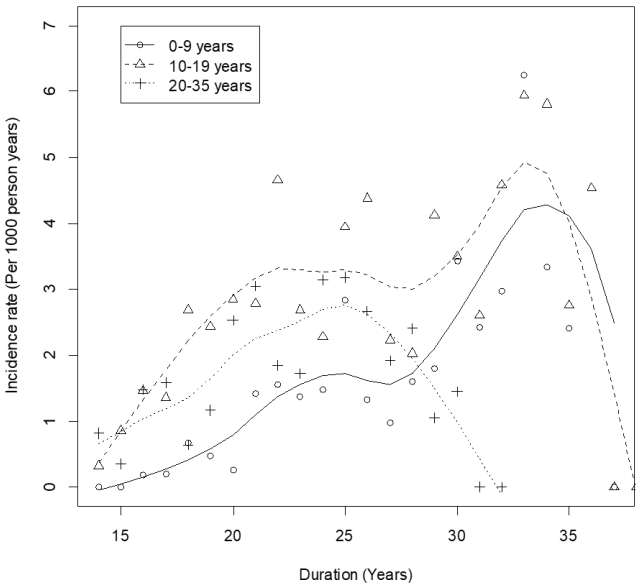

Fig. 7 The cumulative incidence of ESRD at different age at onset of T1D. There seems to be a peak incidence at 33-34 years of T1D but the cases are few with long duration and these data must be interpreted with caution.

Influence of age at onset and sex

We saw no difference related to sex when comparing the separate age at onset groups or when analysing the entire study population.

Regarding age at onset of T1D we found that T1D onset before the age of 10 years yields a lower risk of developing ESRD. When T1D onset is in the age of 20-34 the risk is increased compared to early onset for males but not females. For both sexes, an onset between 10 and 19 is associated with the highest risk fig. 8.

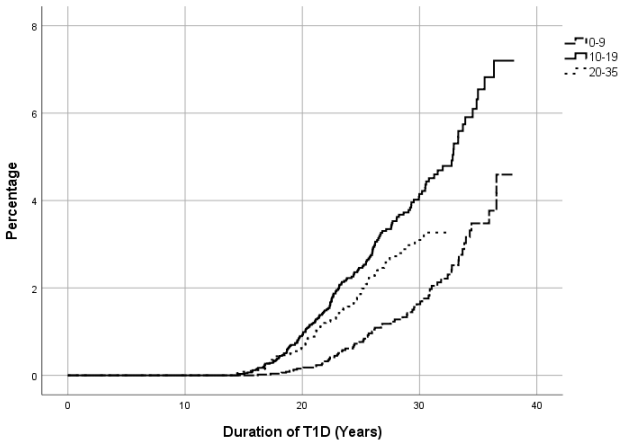

Fig. 8 How the risk of developing ESRD varies according to age at onset of T1D.

The influence of social environment on the risk of developing ESRD (Paper III)

In Paper III the aim was to investigate factors in the social environment during upbringing and early adulthood and their influence on the incidence of ESRD. The analyses included data on an individual level of the patients but also data from both parents separately. The socioeconomic factors of interest were highest achieved educational level and the need of income support. We could not separate the need on an individual level on the parents since the data was designed as having received income support in the household. The study comprised of 9299 patients with T1D duration of more than 14 years. A total of 166 patients had received RRT. The vast majority had T1D as the reported cause of ESRD (n=154), 12 had other kidney diseases causing their ESRD and were excluded from further analysis. Analyses were made on 9287 patients.

Low maternal education was associated with a three folded increase in risk of developing ESRD in the T1D offspring, fig. 9.

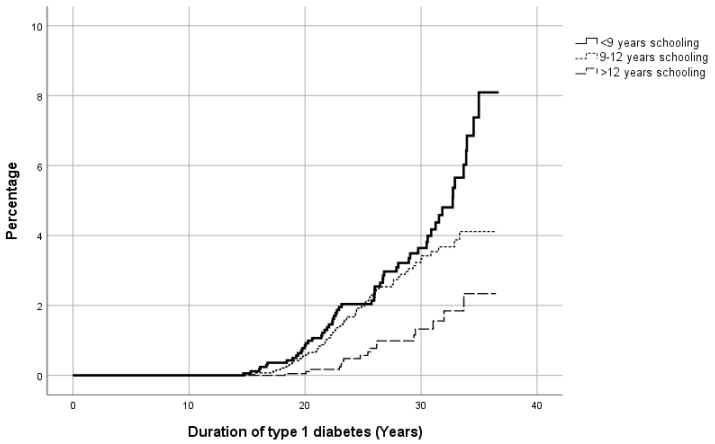

Fig. 9 How the risk of developing ESRD varies according to schooling length of the mother.

Low paternal and T1D individual´s own education showed a doubled and 5 folded increase respectively.

If either parent had ever received income support the risk was 2.6 times higher for developing ESRD, fig. 10.

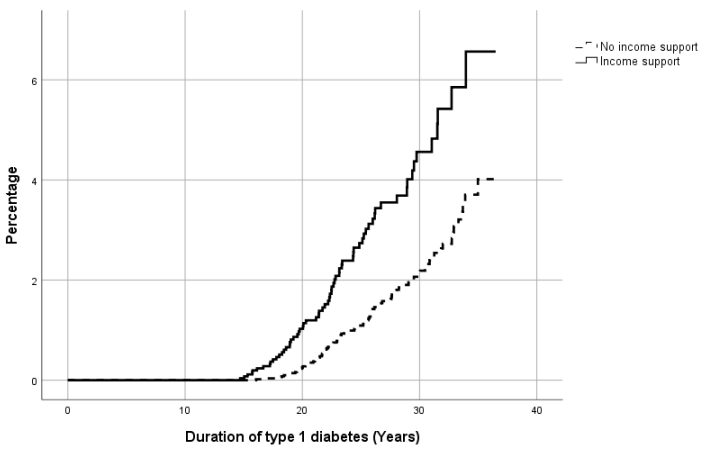

Fig. 10 The risk of the child with T1D to develop ESRD as a function of either or both parents having received income support before the child turned 25 years of age.

More than half of the T1D patients had received income support. We therefore chose to exclude analyses on the patients´ individual level regarding income support. This was done because the data implied that income support and other financial aids such as sick benefits seemed could be intertwined in this population.

When combining the variables in a cox regression adjusted for age at onset of T1D and sex, maternal educational length, parental need of income support as well as T1D individuals own education still were independently associated with risk of developing ESRD. There were no interactions between the studied variables.

Survival in RRT-time trends and treatment choices (Paper IV)

By 31th December 2017, 211 patients in the SCDR had developed ESRD. To study time trends, they were divided into two groups based on the year they started RRT, 1993-2004 or 2005-2017. The division was made to get approximately equal time intervals. Age at onset of RRT, diabetes duration, sex and choice of treatment modality and their relation to survival were analysed.

The median age at start of RRT was 35.4 (22.3-50.2). Age at onset of RRT increased significantly, just as duration of diabetes, when comparing the two periods. Having a macro vascular complication prior to start of RRT was equally common in the time periods. The main cause of death was CVD, followed by CVL.

Choice of treatment

Within two years in RRT, 99 patients were transplanted. When comparing choice of first RRT treatment modality between the different calendar periods, HD decreased and TX increased, but the changes were non-significant. PD remained rather stable. There was a significant increase in deceased donor transplantation between the two calendar year periods. There were no differences between men and women regarding choice of first treatment or being eligible for transplantation.

Survival in RRT

At the end of the study, 65 patients (35.4%) had died, 31 men and 34 women. No significant associations were found between mortality and sex, age at onset of RRT or diabetes duration. The 5 year survival rate was 34.8 and 99.9% respectively for not transplanted and transplanted. The risk of dying was 18 times higher for patients who were never transplanted (95% CI 9.6-33.7).

Adjusted survival

When adjusting for sex, age at onset of RRT and duration of T1D the risk of dying was 2.8 times higher in the period 1993-2004 compared to 2005-2017. For patients starting with HD and PD there was no significant difference in survival between the two periods when patients who were later transplanted were excluded. For patients who were transplanted there was an improvement in survival, fig. 11.

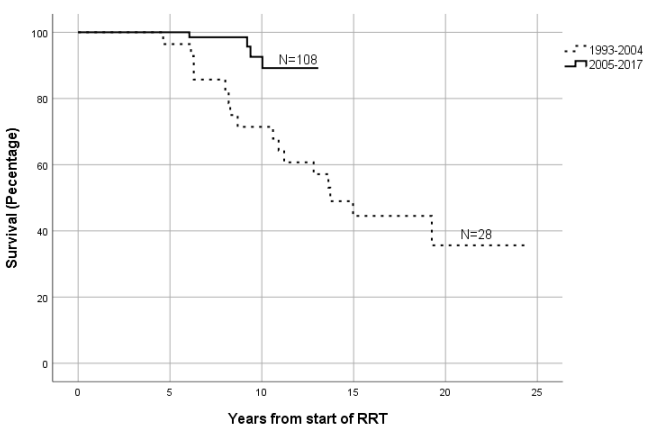

Fig. 11 The association between time period and survival in TX patients.

Having macro vascular disease at start of RRT was significantly associated with death, HR=3.8 (95% CI 2.2-6.5). Not being transplanted within 2 years of start of RRT had an almost 7 fold

increase in risk of dying. The risk was almost twice as high for patients starting on HD when only comparing them to PD, excluding all patients starting with TX. Fig. 12 shows survival based on the first treatment modality.

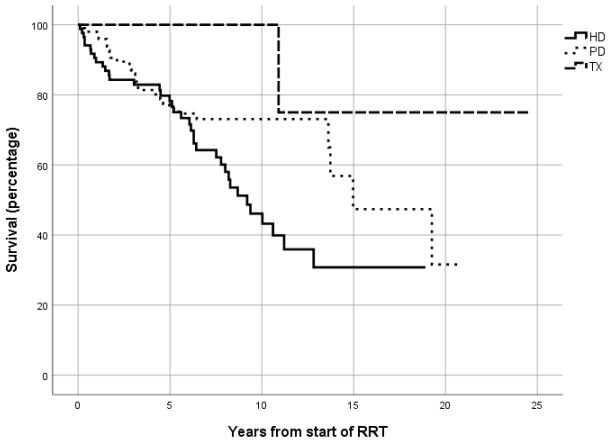

Fig. 12 Survival in in RRT (in years) depending on choice of first treatment. In both the HD and PD group, patients who were later transplanted are included.

Discussion of major findings

ESRD is a serious complication to T1D and to establish more knowledge about its risk factors is important. In this thesis, risk factors that we can consider in the daily clinical setting are investigated. Since ESRD puts a strain on the health care system it is vital to try to foresee the future need of RRT through studies on incidence of and survival in ESRD.

Incidence of ESRD and time trends (Paper I, II)

The incidence of ESRD in the Swedish population remained stable at the same time as ESRD due to T1D decreased, which is encouraging. The reason why the ESRD incidence is stable likely lie in the fact that people live longer, age in itself is related to a decline in kidney function (160). Age is also related to nephrosclerosis and T2D, both more common today as cause of ESRD (138, 161) and also found in our study. The mean age at onset of RRT is increasing and a contributing factor is an acceptance of older patients starting RRT (140). This also drives up the incidence of ESRD.

The study period in Paper I was fairly modern, 1995-2010 but still a decrease in incidence of ESRD was found. A contemporary study from Denmark showed no decrease in incidence of ESRD due to T1D between 2000-2004 (162). Most patients in both studies would have had a T1D onset before the mid 80´s, related to the knowledge that it takes about 25 years to develop ESRD. So maybe what we see in our study is merely a delay in onset of ESRD due to the introduction of ACE inhibitors and later AII blockers. But since we don´t know the duration of T1D we can´t know with certainty if it is treatment or duration of T1D that differs over time.

It is well established that duration of T1D is a major risk factor for the development of late complications. In Paper II we found the same decrease in incidence over time as in Paper I but now data were adjusted for T1D duration. Since Sweden has a high incidence of T1D, strict national guidelines were issued in the early to mid

80ies, stating intensive treatment is advocated (163-165). Most of the patients in this study would therefore be subjected to them (T1D onset after 1978). This means that most of the patients would have benefitted from reno-protective medicines such as ACE inhibitors, A2-blocker and statins, at least for a substantial number of years. The T1D specific treatment would be multiple daily injections rendering possibilities for better metabolic control. Even so, we found a significant decrease over time.

We did not find any difference between males and females in risk of developing ESRD in Paper II, neither in the whole study population nor within the age at onset groups. Data on the subject is diverging, with some suggesting no difference (71, 166, 167) but also some showing a male preponderance (69, 70). Perhaps we are looking at the question from the wrong perspective. Studies have shown that females with T1D have a more pronounced excess risk of CVD compared to males with T1D (168). A higher incidence and a faster rate of progression of renal disease have been described in T1D females compared to females with non-diabetic renal disease (67). In Paper I we found that females with T1D developed ESRD earlier than males, for T2D the opposite was seen, males developing ESRD earlier. The male to female ratio is higher in non-diabetic ESRD than in the T1D group. At the same time T1D is more common in males. So perhaps our focus should be on the relative over risk for females and be more aggressive in our treatment. Studies have shown a more favourable outcome on RAAS blockade on progression in renal disease for females than males (169). In that context it is of interest that in the SCDR population, RAAS blockade is more seldom prescribed to females, even with microalbuminuria present (unpublished data from the study group), a prescription pattern also reported in another Swedish study, not only on patients with diabetes though (170).

We saw the same relation between age at onset and risk as have been reported by others (48, 68-71, 171). Explanatory speculations have been the imbalance in sex and growth hormones in puberty, leading to insulin resistance and affecting metabolic control (67, 101, 172). Higher mean HbA1c have been found in this age group

(173). More psychological strain on the T1D patient and their parents was found during adolescence compared to earlier years, regardless of years with T1D, and this correlated to a worsening of the metabolic control (174). Other postulated explanations are that getting the disease early makes the patient and the family acquainted to the disease and its management.

So, have we now got the tools to prevent ESRD or do we just delay the progression? There are risk factors beyond our control (at least today) such as genetic factors. There are also lifestyle factors that increase the risk such as overweight and smoking, well known to be hard to change.

A few years ago we reported on a low ESRD incidence (3.3%) after 30 years of T1D (68). Now we added another 8 years of follow up to the study and still found a very low incidence of 5.6%. This is in accordance with studies from Norway published last year, also in a younger population, and with lower incidence than formerly reported (70, 71). We found that the age at onset of RRT for T1D patients had increased by three years, a change not seen in the other causes of ESRD, including T2D. This could imply a preventive effect of intensive treatment but is most likely a delaying effect. We did see that the incidence of ESRD seemed to decrease with longer T1D duration (>35 years) but the data were scarce here and so must be interpreted with caution. It was proposed many years ago that with increasing duration of T1D the incidence of ESRD goes down (48, 49). Our results suggests that the hypothesis might stand but that a delay have occurred. It has been speculated that patients developing ESRD early have a genetic predisposition towards DN and that the late developers might be those with less strict metabolic control. In our data we do not have information on HbA1c, lipid levels or blood pressure. This is of course a disadvantage as we do not know if there are differences in clinical parameters that explain our results. According to yearly reports from NDR the change in these parameters over the study period is small however. Technical advances in diabetic care have in recent years been impressive with continuous glucose measurement, flash glucose measurement and

of course insulin pumps. New integrated insulin pumps are just being introduced on the market where the dosing of insulin is based on fully automated algorithms, a closed-loop system. The effect of these devices on the incidence of complications will take years to evaluate but will without a doubt improve the life of the T1D patients and their risk for complications substantially.

Socioeconomic status as a risk factor (Paper III)

Childhood onset T1D is a disease affecting the entire family of the patient, not only because of the constant need for making treatment choices but also in other aspects. Although not a disease which can be treated by dietary regiments such as T2D, dietary issues are raised and can afflict the family´s eating and lifestyle habits. To appreciate and adhere to the information, pre-knowledge of the disease, it´s management and the factors influencing blood glucose levels are needed. During childhood it is only natural that parents or other caregivers take more responsibility for the management of T1D. Therefore our results showing an increased risk for development of ESRD when parents have a limited education is not surprising. Other studies have shown similar results (121, 122, 125, 175). Parents and their help are needed also in adolescence. A positive, supporting climate in the home as well as a less restrictive parenting style; additionally having a partner to share the burden with, all have a positive effect on the risk of developing ESRD (113, 176, 177).

A study focusing on the pre-knowledge about complications in parents and youths showed an association only with the youths knowledge and associated adherence to treatment (177). We found a similar result in our study with a large effect of the patients own educational level although the effect of the mother´s education remained in the additive model.

We also found an association between parental need of income support and the child's risk to develop ESRD. We choose need of income support because we found it to be a better indication of social vulnerability than income. Many parents could work part

time, benefit from parental leave or have other income sources besides work which affect their income level. Families in need of income support are under more stress due to many factors, lack of money being one issue. Unemployment and receiving health care allowance with a concurrent social isolation for all family members are more prevalent in families with lower SES (178).

To even out financial inequalities, the Swedish health care system gives all children under 18 years free access to medical care and since 1 January 2016 also free prescription medicine. For all patients with T1D, regardless of age, all medical devices related to diabetes care as well as insulin are free of charge. Studies from countries with other health care systems have shown that money matters, for example two studies from the United States (179, 180). Reports from other countries also show a clear association between lower SES and risk of later complications (122, 181) as well as death (118, 119, 121, 182). Studies have also shown that the T1D patients have lower income and are more often unemployed compared to healthy controls (183, 184), which could be additive to their risk.

One might speculate that the higher risk in the lower SES group will decrease with time in Sweden since all families have free access to all medicine including ACE-inhibitors, AII blockers and statins. But the impact that free medicine has on risk would likely be small as indicated in studies were the lower SES also is correlated to worsening of metabolic control (185), obesity as well as an unhealthy lifestyle including smoking habits (114, 186). A large study from the WHO showed that there was a correlation between a country´s health care system, gross national investment and purchasing power and the development of T1D complications, even after adjusting for HbA1c levels and hypertension (187). SES level even seems to be an independent risk factor for the development of ESRD (137).

So what are the implications related to this knowledge? The Swedish social welfare system has a well-developed safety net but it still does not prevent differences between SES levels.

To take the time to assess the pre-knowledge of the patients and their families is essential. All T1D children in Sweden attends hospital based diabetes clinics, meeting up with a specialised nurse and a doctor four times a year. We found that it is the patient´s own educational level that has the strongest influence on future risk of developing ESRD. We interpreted this as the ability to understand, learn about and adhere to the treatment. It has been shown that focusing on patients with less knowledge and low adherence to treatment can yield as good results (HbA1c levels) as in patients with better understanding of disease management beforehand (188). To continue to establish the patient´s understanding of and attitude towards his/her disease is crucial, both in children and in the adult patients. This is not always the case as shown in a study from Sweden on diabetes health care professionals (189). And maybe it is even more important in the adult clinics to consider since now the patients have to pay for medications themselves (except insulin) and therefore need to understand the rationale behind them.

Survival in RRT (Paper IV)

We found a significant decrease in risk of death between those starting RRT in 1993-2004 compared to 2005-2017. At the same time we did not find a significant change in number of patients receiving a kidney transplant. Being transplanted had the best survival and in the later period none of the patients being transplanted had died. That TX is related to the longest survival is not surprising. TX is also associated with better survival than patients remaining on the waiting list for transplantation, even though they are comparable in health and age (149). Studies have also shown that in particular young patients with diabetes benefit from TX (152) A Swedish study published 2018 showed that TX was associated with a higher possibility to return to the workforce, generate a higher income and for less frequent early retirement (145).

We found an increase in the use of marginal and deceased donors which is positive since it increases the pool of available organs. It

has long been one of the limiting factors for kidney transplantation. The fact that there was no difference in survival due to donor source was probably related to statistical power issues.

It is positive that we did not find any differences between number of males and females being transplanted, nor in survival overall between gender.

Macro vascular entities were prevalent among many of these young patients. They also showed an association with death which is in accordance with other studies (139, 151, 190). CVD was the most common cause of death. Other studies have also shown a relation between comorbidities and death (139, 151). This further strengthens the implications to treat risk factors for vascular disease with statins and BP medicine early on in T1D.

A Limitation to this study is the short follow up for many of the patients. We tried to adjust for this by doing subgroup analyses on patients with an onset before 1 January 2013. The results were the same. Another limitation is the small number of patients which could influence our results where few patients with outlying results could have great impact.

The median survival was 8.2 years in the early group and in the later more than 50 % were still alive so no median survival could be calculated. No TX patient in 2005-2017 had died at the end of study and 80 % of the patients from this period were alive by 31 December 2017. Why we do see a decrease in risk between the two time periods are uncertain. A natural explanation would be an increase in TX but although we saw an increase it was not significant. Studies have shown an increased survival in RRT for the entire RRT population (140, 150) as well as for T1D (148). This has mainly been due to a better preventive treatment of cardiovascular risk factors and hence lower mortality in CVD (140, 150). We did not know the treatment for comorbidities in our study but we did see a non-significant decrease in prevalent comorbidities entering RRT which could partly explain the results.

Conclusion

- The incidence of ESRD remains stable in Sweden. In contrast, the incidence of ESRD due to T1D is decreasing over the last decades. The T1D patients entering RRT are now 3 years older. This is in discrepancy to the ESRD population as a whole and the T2D population.
- The incidence of ESRD is low in Sweden after almost 40 years of duration. Even in this group where almost all patients have benefitted from modern day diabetes treatment we still see a decrease in incident ESRD cases over the years.
- The patients' educational level strongly influence the risk of them later developing ESRD. Parental SES level (education and need of social support) also affects the risk, with low SES rendering a higher risk for the patient. This is important to remember in the clinical setting, acknowledging different educational strategies about T1D in different families.
- The survival in RRT for T1D patients with childhood onset have increased with more recent onset of ESRD. As expected, transplantation is correlated with the best survival and more than half of the patients are transplanted at least once. There are no differences between sexes in survival or transplantation rate.

In conclusion we found an encouraging trend in the incidence of ESRD due to T1D with time and still a very low cumulative incidence of ESRD. The patients with T1D enter RRT at least three years later in life. Both in the incidence of and survival with ESRD we could not find any differences between sexes. The fact that SES is an important risk factor is noteworthy and something that needs to be highlighted in the clinical setting and appointments with the patients and their families.

Thoughts for the future

We found a declining incidence of ESRD after 35 years of T1D, 10 years later than earlier studies have implied. The cases with that long follow up were few though. To see if we have found a peak incidence and not just a decrease due to lack of data would be interesting.

The survival in RRT has increased but our population is small, with only 211 patients. The patients are also fairly young since their T1D onset was before 15 years of age. To conduct the same study but with all T1D patients in RRT could maybe change our results or strengthen our conclusions.

There have been reports of differences in TX rate and survival in the general RRT population related to SES level (191-193). This is also an issue that needs more focus in the childhood onset T1D population.

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References

1. American Diabetes A. (2) Classification and diagnosis of diabetes. Diabetes Care. 2015;38 Suppl:S8-S16.

2. Consultation Who. Definition and diagnosis of diabetes and intermediate hyperglycaemia 2006 [Available from: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf.

3. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. Diabetes. 2017;66(2):241-55.

4. Eisenbarth GS. Update in type 1 diabetes. J Clin Endocrinol Metab. 2007;92(7):2403-7.

5. Notkins AL, Lernmark A. Autoimmune type 1 diabetes: resolved and unresolved issues. J Clin Invest. 2001;108(9):1247-52.

6. Noble JA, Valdes AM, Varney MD, Carlson JA, Moonsamy P, Fear AL, et al. HLA class I and genetic susceptibility to type 1 diabetes: results from the Type 1 Diabetes Genetics Consortium. Diabetes. 2010;59(11):2972-9.

7. Ilonen J, Sjoroos M, Knip M, Veijola R, Simell O, Akerblom HK, et al. Estimation of genetic risk for type 1 diabetes. Am J Med Genet. 2002;115(1):30-6.

8. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. A study of 200 pairs. Diabetologia. 1981;20(2):87-93.

9. Kaprio J, Tuomilehto J, Koskenvuo M, Romanov K, Reunanen A, Eriksson J, et al. Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia. 1992;35(11):1060-7.

10. Nystrom L, Dahlquist G, Rewers M, Wall S. The Swedish childhood diabetes study. An analysis of the temporal variation in diabetes incidence 1978-1987. Int J Epidemiol. 1990;19(1):141-6.

11. Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK. Environmental triggers and determinants of type 1 diabetes. Diabetes. 2005;54 Suppl 2:S125-36.

12. Akerblom HK, Knip M. Putative environmental factors in Type 1 diabetes. Diabetes Metab Rev. 1998;14(1):31-67.

13. Jaeckel E, Manns M, Von Herrath M. Viruses and diabetes. Ann N Y Acad Sci. 2002;958:7-25.

14. Schneider DA, von Herrath MG. Potential viral pathogenic mechanism in human type 1 diabetes. Diabetologia. 2014;57(10):2009-18.

15. Roivainen M, Klingel K. Virus infections and type 1 diabetes risk. Curr Diab Rep. 2010;10(5):350-6.

16. Wahlberg J, Vaarala O, Ludvigsson J, group AB-s. Dietary risk factors for the emergence of type 1 diabetes-related autoantibodies in 21/2 year-old Swedish children. The British journal of nutrition. 2006;95(3):603-8.

17. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. 2002;347(12):911-20.

18. Bloomfield SF, Rook GA, Scott EA, Shanahan F, Stanwell-Smith R, Turner P. Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. Perspect Public Health. 2016;136(4):213-24.

19. Scudellari M. News Feature: Cleaning up the hygiene hypothesis. Proc Natl Acad Sci U S A. 2017;114(7):1433-6.

20. Hara N, Alkanani AK, Ir D, Robertson CE, Wagner BD, Frank DN, et al. The role of the intestinal microbiota in type 1 diabetes. Clin Immunol. 2013;146(2):112-9.

21. Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. Diabetologia. 2006;49(1):20-4.

22. Johansson C, Samuelsson U, Ludvigsson J. A high weight gain early in life is associated with an increased risk of type 1 (insulin-dependent) diabetes mellitus. Diabetologia. 1994;37(1):91-4.

23. Ljungkrantz M, Ludvigsson J, Samuelsson U. Type 1 diabetes: increased height and weight gains in early childhood. Pediatric diabetes. 2008;9(3 Pt 2):50-6.

24. Patterson CC, Dahlquist G, Soltesz G, Green A, Europe EASG, Diabetes. Is childhood-onset type I diabetes a wealth-related disease? An ecological analysis of European incidence rates. Diabetologia. 2001;44 Suppl 3:B9-16.

25. Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015;38(10):1964-74.

26. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabetic medicine : a journal of the British Diabetic Association. 2006;23(8):857-66.

27. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of Type I diabetes--the analysis of the data on published incidence trends. Diabetologia. 1999;42(12):1395-403.

28. Dahlquist G, Blom L, Holmgren G, Hagglof B, Larsson Y, Sterky G, et al. The epidemiology of diabetes in Swedish children 0-14 years--a six-year prospective study. Diabetologia. 1985;28(11):802-8.

29. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009;373(9680):2027-33.

30. Njurmedicin. Stockholm: Liber AB; 2008.

31. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clinical journal of the American Society of Nephrology : CJASN. 2017;12(12):2032-45.

32. Najafian B, Mauer M. Progression of diabetic nephropathy in type 1 diabetic patients. Diabetes Res Clin Pract. 2009;83(1):1-8.

33. Najafian B, Alpers CE, Fogo AB. Pathology of human diabetic nephropathy. Contrib Nephrol. 2011;170:36-47.

34. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol. 2007;27(2):195-207.

35. Kimmelstiel P, Wilson C. Intercapillary Lesions in the Glomeruli of the Kidney. Am J Pathol. 1936;12(1):83-98 7.

36. Conti S, Perico N, Novelli R, Carrara C, Benigni A, Remuzzi G. Early and late scanning electron microscopy findings in diabetic kidney disease. Sci Rep. 2018;8(1):4909.

37. Adler S. Diabetic nephropathy: Linking histology, cell biology, and genetics. Kidney Int. 2004;66(5):2095-106.

38. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes. 2003;52(4):1036-40.

39. Bangstad HJ, Osterby R, Dahl-Jorgensen K, Berg KJ, Hartmann A, Nyberg G, et al. Early glomerulopathy is present in young, type 1 (insulin-dependent) diabetic patients with microalbuminuria. Diabetologia. 1993;36(6):523-9.

40. Chavers BM, Bilous RW, Ellis EN, Steffes MW, Mauer SM. Glomerular lesions and urinary albumin excretion in type I diabetes without overt proteinuria. N Engl J Med. 1989;320(15):966-70.

41. Krolewski AS, Niewczas MA, Skupien J, Gohda T, Smiles A, Eckfeldt JH, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care. 2014;37(1):226-34.

42. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. Diabetes. 1983;32 Suppl 2:64-78.

43. Fioretto P, Steffes MW, Mauer M. Glomerular structure in nonproteinuric IDDM patients with various levels of albuminuria. Diabetes. 1994;43(11):1358-64.

44. Molitch ME, Steffes M, Sun W, Rutledge B, Cleary P, de Boer IH, et al. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care. 2010;33(7):1536-43.

45. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003;348(23):2285-93.

46. de Boer IH, Afkarian M, Rue TC, Cleary PA, Lachin JM, Molitch ME, et al. Renal outcomes in patients with type 1 diabetes and macroalbuminuria. J Am Soc Nephrol. 2014;25(10):2342-50.

47. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17-28.

48. Krolewski AS, Warram JH, Christlieb AR, Busick EJ, Kahn CR. The changing natural history of nephropathy in type I diabetes. Am J Med. 1985;78(5):785-94.

49. Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in Type 1 (insulin-dependent) diabetes: an epidemiological study. Diabetologia. 1983;25(6):496-501.

50. Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. BMJ. 2004;328(7448):1105.

51. Cobas RA, Santos B, da Silva PC, Neves R, Gomes MB. Progression to microalbuminuria in patients with type 1 diabetes: a seven-year prospective study. Diabetol Metab Syndr. 2011;3:21.

52. Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: a 10-year prospective observational study. Diabetes Care. 2002;25(5):859-64.

53. Freedman BI, Bostrom M, Daeihagh P, Bowden DW. Genetic factors in diabetic nephropathy. Clinical journal of the American Society of Nephrology : CJASN. 2007;2(6):1306-16.

54. Lee YH, Song GG. Genome-wide pathway analysis for diabetic nephropathy in type 1 diabetes. Endocr Res. 2016;41(1):21-7.

55. Pezzolesi MG, Poznik GD, Mychaleckyj JC, Paterson AD, Barati MT, Klein JB, et al. Genome-wide association scan for diabetic nephropathy susceptibility genes in type 1 diabetes. Diabetes. 2009;58(6):1403-10.

56. Sambo F, Malovini A, Sandholm N, Stavarachi M, Forsblom C, Makinen VP, et al. Novel genetic susceptibility loci for diabetic end-stage renal disease identified through robust naive Bayes classification. Diabetologia. 2014;57(8):1611-22.

57. Sandholm N, Van Zuydam N, Ahlqvist E, Juliusdottir T, Deshmukh HA, Rayner NW, et al. The Genetic Landscape of Renal Complications in Type 1 Diabetes. J Am Soc Nephrol. 2017;28(2):557-74.

58. Mollsten A, Wessman M, Svensson M, Forsblom C, Parkkonen M, Brismar K, et al. Glu298Asp and NOS4ab polymorphisms in diabetic nephropathy. Ann Med. 2006;38(7):522-8.

59. Thorn LM, Forsblom C, Fagerudd J, Pettersson-Fernholm K, Kilpikari R, Groop PH, et al. Clustering of risk factors in parents of patients with type 1 diabetes and nephropathy. Diabetes Care. 2007;30(5):1162-7.

60. Earle K, Walker J, Hill C, Viberti G. Familial clustering of cardiovascular disease in patients with insulin-dependent diabetes and nephropathy. N Engl J Med. 1992;326(10):673-7.

61. Fagerudd JA, Pettersson-Fernholm KJ, Gronhagen-Riska C, Groop PH. The impact of a family history of Type II (non-insulin-dependent) diabetes mellitus on the risk of diabetic nephropathy in patients with Type I (insulin-dependent) diabetes mellitus. Diabetologia. 1999;42(5):519-26.

62. Snieder H, Sawtell PA, Ross L, Walker J, Spector TD, Leslie RD. HbA(1c) levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. Diabetes. 2001;50(12):2858-63.

63. Silbiger SR, Neugarten J. The impact of gender on the progression of chronic renal disease. Am J Kidney Dis. 1995;25(4):515-33.

64. Evans M, Fryzek JP, Elinder CG, Cohen SS, McLaughlin JK, Nyren O, et al. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. Am J Kidney Dis. 2005;46(5):863-70.

65. Xu Q Fau - Wells CC, Wells Cc Fau - Garman JH, Garman Jh Fau - Asico L, Asico L Fau - Escano CS, Escano Cs Fau - Maric C, Maric C. Imbalance in sex hormone levels exacerbates diabetic renal disease. (1524-4563 (Electronic)).

66. Wells CC, Riazi S, Mankhey RW, Bhatti F, Ecelbarger C, Maric C. Diabetic nephropathy is associated with decreased circulating estradiol levels and imbalance in the expression of renal estrogen receptors. Gend Med. 2005;2(4):227-37.

67. Maric C. Sex, diabetes and the kidney. American journal of physiology Renal physiology. 2009;296(4):F680-8.

68. Mollsten A, Svensson M, Waernbaum I, Berhan Y, Schon S, Nystrom L, et al. Cumulative risk, age at onset, and sex-specific differences for developing end-stage renal disease in young patients with type 1 diabetes: a nationwide population-based cohort study. Diabetes. 2010;59(7):1803-8.

69. Harjutsalo V, Maric C, Forsblom C, Thorn L, Waden J, Groop PH. Sex-related differences in the long-term risk of microvascular complications by age at onset of type 1 diabetes. Diabetologia. 2011;54(8):1992-9.

70. Gagnum V, Saeed M, Stene LC, Leivestad T, Joner G, Skrivarhaug T. Low Incidence of End-Stage Renal Disease in Childhood-Onset Type 1 Diabetes Followed for Up to 42 Years. Diabetes Care. 2017.

71. Gagnum V, Stene LC, Leivestad T, Joner G, Skrivarhaug T. Long-term Mortality and End-Stage Renal Disease in a Type 1 Diabetes Population Diagnosed at Age 15-29 Years in Norway. Diabetes Care. 2017;40(1):38-45.

72. Vasylyeva TL, Ferry JRJ. Novel roles of the IGF-IGFBP axis in etiopathophysiology of diabetic nephropathy. Diabetes Research and Clinical Practice. 2007;76(2):177-86.

73. Kumar PA, Brosius FC, 3rd, Menon RK. The glomerular podocyte as a target of growth hormone action: implications for the pathogenesis of diabetic nephropathy. Curr Diabetes Rev. 2011;7(1):50-5.

74. Amin R, Schultz C, Ong K, Frystyk J, Dalton RN, Perry L, et al. Low IGF-I and elevated testosterone during puberty in subjects with type 1 diabetes developing microalbuminuria in comparison to normoalbuminuric control subjects: the Oxford Regional Prospective Study. Diabetes Care. 2003;26(5):1456-61.

75. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53.

76. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995;44(8):968-83.

77. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329(5):304-9.

78. Diabetes C, Complications Trial Research G, Nathan DM, Genuth S, Lachin J, Cleary P, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.

79. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA. 2003;290(16):2159-67.

80. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854-65.

81. Samuelsson U, Steineck I, Gubbjornsdottir S. A high mean-HbA1c value 3-15 months after diagnosis of type 1 diabetes in childhood is related to metabolic control, macroalbuminuria, and retinopathy in early adulthood--a pilot study using two nation-wide population based quality registries. Pediatric diabetes. 2014;15(3):229-35.

82. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. Diabetes Care. 2004;27(4):955-62.

83. Waden J, Forsblom C, Thorn LM, Gordin D, Saraheimo M, Groop PH, et al. A1C variability predicts incident cardiovascular events, microalbuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. Diabetes. 2009;58(11):2649-55.

84. Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J. Good glycemic control remains crucial in prevention of late diabetic complications--the Linkoping Diabetes Complications Study. Pediatric diabetes. 2009;10(3):168-76.

85. Larkins RG, Dunlop ME. The link between hyperglycaemia and diabetic nephropathy. Diabetologia. 1992;35(6):499-504.

86. Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. Am J Kidney Dis. 2018;71(6):884-95.

87. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998;317(7160):703-13.

88. Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol. 2005;16(10):3027-37.

89. Socialstyrelsen. Nationella riktlinjer för diabetesvård 2017 [Available from: https://www.socialstyrelsen.se/nationellariktlinjerfordiabetesvard.

90. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329(20):1456-62.

91. Ogawa S, Matsushima M, Mori T, Okamura M, Senda M, Sakamoto T, et al. Identification of the stages of diabetic nephropathy at which angiotensin II receptor blockers most effectively suppress albuminuria. Am J Hypertens. 2013;26(9):1064-9.

92. Rossing K, Jacobsen P, Pietraszek L, Parving HH. Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: a randomized double-blind crossover trial. Diabetes Care. 2003;26(8):2268-74.

93. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870-8.

94. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. The EUCLID Study Group. Lancet. 1997;349(9068):1787-92.

95. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med. 2009;361(1):40-51.

96. Marcovecchio ML, Chiesa ST, Bond S, Daneman D, Dawson S, Donaghue KC, et al. ACE Inhibitors and Statins in Adolescents with Type 1 Diabetes. N Engl J Med. 2017;377(18):1733-45.

97. Mann JF, Anderson C, Gao P, Gerstein HC, Boehm M, Ryden L, et al. Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: results of the ONTARGET trial. J Hypertens. 2013;31(2):414-21.

98. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372(9638):547-53.

99. Mollsten A, Kockum I, Svensson M, Rudberg S, Ugarph-Morawski A, Brismar K, et al. The effect of polymorphisms in the renin-angiotensin-aldosterone system on diabetic nephropathy risk. J Diabetes Complications. 2008;22(6):377-83.

100. Ha SK. ACE insertion/deletion polymorphism and diabetic nephropathy: clinical implications of genetic information. J Diabetes Res. 2014;2014:846068.

101. Harjutsalo V, Groop PH. Epidemiology and risk factors for diabetic kidney disease. Adv Chronic Kidney Dis. 2014;21(3):260-6.

102. Raile K, Galler A, Hofer S, Herbst A, Dunstheimer D, Busch P, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. Diabetes Care. 2007;30(10):2523-8.

103. Jenkins AJ, Lyons TJ, Zheng D, Otvos JD, Lackland DT, McGee D, et al. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int. 2003;64(3):817-28.

104. Thomas MC, Rosengard-Barlund M, Mills V, Ronnback M, Thomas S, Forsblom C, et al. Serum lipids and the progression of nephropathy in type 1 diabetes. Diabetes Care. 2006;29(2):317-22.

105. Tolonen N, Forsblom C, Thorn L, Waden J, Rosengard-Barlund M, Saraheimo M, et al. Relationship between lipid profiles and kidney function in patients with type 1 diabetes. Diabetologia. 2008;51(1):12-20.

106. Marcovecchio ML, Dalton RN, Prevost AT, Acerini CL, Barrett TG, Cooper JD, et al. Prevalence of abnormal lipid profiles and the relationship with the development of microalbuminuria in adolescents with type 1 diabetes. Diabetes Care. 2009;32(4):658-63.

107. Petitti DB, Imperatore G, Palla SL, Daniels SR, Dolan LM, Kershnar AK, et al. Serum lipids and glucose control: the SEARCH for Diabetes in Youth study. Arch Pediatr Adolesc Med. 2007;161(2):159-65.

108. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-96.

109. Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of

cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005-16.

110. Cholesterol Treatment Trialists C, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-25.

111. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238-48.

112. Tahirovic H, Toromanovic A. Glycemic control in diabetic children: role of mother's knowledge and socioeconomic status. European journal of pediatrics. 2010;169(8):961-4.

113. Swift EE, Chen R, Hershberger A, Holmes CS. Demographic risk factors, mediators, and moderators in youths' diabetes metabolic control. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine. 2006;32(1):39-49.

114. Overstreet S, Holmes CS, Dunlap WP, Frentz J. Sociodemographic risk factors to disease control in children with diabetes. Diabetic medicine : a journal of the British Diabetic Association. 1997;14(2):153-7.

115. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ. 2011;343:d4092.

116. Sayers A, Thayer D, Harvey JN, Luzio S, Atkinson MD, French R, et al. Evidence for a persistent, major excess in all cause admissions to hospital in children with type-1 diabetes: results from a large Welsh national matched community cohort study. BMJ open. 2015;5(4):e005644.

117. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ. Association of socioeconomic status with mortality in type 1 diabetes: the Pittsburgh epidemiology of diabetes complications study. Annals of epidemiology. 2011;21(5):367-73.

118. Rawshani A, Svensson AM, Rosengren A, Eliasson B, Gudbjornsdottir S. Impact of Socioeconomic Status on Cardiovascular Disease and Mortality in 24,947 Individuals With Type 1 Diabetes. Diabetes Care. 2015;38(8):1518-27.

119. Berhan YT, Eliasson M, Mollsten A, Waernbaum I, Dahlquist G. Impact of parental socioeconomic status on excess mortality in a population-based cohort of subjects with childhood-onset type 1 diabetes. Diabetes Care. 2015;38(5):827-32.

120. Cooper MN, de Klerk NH, Jones TW, Davis EA. Clinical and demographic risk factors associated with mortality during early adulthood in a population-based cohort of childhood-onset type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2014;31(12):1550-8.

121. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ. Associations between socioeconomic status and major complications in type 1 diabetes: the Pittsburgh epidemiology of diabetes complication (EDC) Study. Annals of epidemiology. 2011;21(5):374-81.

122. Collier A, Ghosh S, Hair M, Waugh N. Impact of socioeconomic status and gender on glycaemic control, cardiovascular risk factors and diabetes complications in type 1 and 2 diabetes: a population based analysis from a Scottish region. Diabetes & metabolism. 2015;41(2):145-51.

123. Poulton R, Caspi A, Milne BJ, Thomson WM, Taylor A, Sears MR, et al. Association between children's experience of socioeconomic disadvantage and adult health: a life-course study. Lancet. 2002;360(9346):1640-5.

124. Hallerod B, Gustafsson JE. A longitudinal analysis of the relationship between changes in socio-economic status and changes in health. Soc Sci Med. 2011;72(1):116-23.

125. Chaturvedi N, Stephenson JM, Fuller JH. The relationship between socioeconomic status and diabetes control and complications in the EURODIAB IDDM Complications Study. Diabetes Care. 1996;19(5):423-30.

126. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O. Obesity and risk for chronic renal failure. J Am Soc Nephrol. 2006;17(6):1695-702.

127. Vivante A, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Arch Intern Med. 2012;172(21):1644-50.

128. Ritz E. Obesity and CKD: how to assess the risk? Am J Kidney Dis. 2008;52(1):1-6.

129. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144(1):21-8.

130. Ejerblad E, Fored CM, Lindblad P, Fryzek J, Dickman PW, Elinder CG, et al. Association between smoking and chronic renal failure in a nationwide population-based case-control study. J Am Soc Nephrol. 2004;15(8):2178-85.

131. Feodoroff M, Harjutsalo V, Forsblom C, Thorn L, Waden J, Tolonen N, et al. Smoking and progression of diabetic nephropathy in patients with type 1 diabetes. Acta Diabetol. 2016;53(4):525-33.

132. Landray MJ, Emberson JR, Blackwell L, Dasgupta T, Zakeri R, Morgan MD, et al. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. Am J Kidney Dis. 2010;56(6):1082-94.

133. Brennan SL, Henry MJ, Nicholson GC, Kotowicz MA, Pasco JA. Socioeconomic status and risk factors for obesity and metabolic disorders in a population-based sample of adult females. Preventive medicine. 2009;49(2-3):165-71.

134. Schumann B, Kluttig A, Tiller D, Werdan K, Haerting J, Greiser KH. Association of childhood and adult socioeconomic indicators with cardiovascular risk factors and its modification by age: the CARLA Study 2002-2006. BMC Public Health. 2011;11:289.

135. Steptoe A, Shamaei-Tousi A, Gylfe A, Henderson B, Bergstrom S, Marmot M. Socioeconomic status, pathogen burden and cardiovascular disease risk. Heart. 2007;93(12):1567-70.

136. Brodersen NH, Steptoe A, Boniface DR, Wardle J. Trends in physical activity and sedentary behaviour in adolescence: ethnic and socioeconomic differences. British journal of sports medicine. 2007;41(3):140-4.

137. Fored CM, Ejerblad E, Fryzek JP, Lambe M, Lindblad P, Nyren O, et al. Socio-economic status and chronic renal failure: a population-based case-control study in Sweden. Nephrol Dial Transplant. 2003;18(1):82-8.

138. Schon S, Ekberg H, Wikstrom B, Oden A, Ahlmen J. Renal replacement therapy in Sweden. Scand J Urol Nephrol. 2004;38(4):332-9.

139. Brunner FP, Brynger H, Challah S, Fassbinder W, Geerlings W, Selwood NH, et al. Renal replacement therapy in patients with diabetic nephropathy, 1980-1985. Report from the European Dialysis and Transplant Association Registry. Nephrol Dial Transplant. 1988;3(5):585-95.

140. Van Dijk PC, Jager KJ, Stengel B, Gronhagen-Riska C, Feest TG, Briggs JD. Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991-2000). Kidney Int. 2005;67(4):1489-99.

141. Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. JAMA. 2005;294(14):1782-7.

142. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes. 2006;55(5):1463-9.

143. Costacou T, Orchard TJ. Cumulative Kidney Complication Risk by 50 Years of Type 1 Diabetes: The Effects of Sex, Age, and Calendar Year at Onset. Diabetes Care. 2017.

144. Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. 2009;169(14):1307-16.

145. Jarl J, Gerdtham UG, Desatnik P, Prutz KG. Effects of Kidney Transplantation on Labor Market Outcomes in Sweden. Transplantation. 2018;102(8):1375-81.

146. Kussman MJ, Goldstein H, Gleason RE. The clinical course of diabetic nephropathy. JAMA. 1976;236(16):1861-3.

147. Bell S, Fletcher EH, Brady I, Looker HC, Levin D, Joss N, et al. End-stage renal disease and survival in people with diabetes: a national database linkage study. QJM : monthly journal of the Association of Physicians. 2015;108(2):127-34.

148. Haapio M, Helve J, Groop PH, Gronhagen-Riska C, Finne P. Survival of patients with type 1 diabetes receiving renal replacement therapy in 1980-2007. Diabetes Care. 2010;33(8):1718-23.

149. Sorensen VR, Mathiesen ER, Heaf J, Feldt-Rasmussen B. Improved survival rate in patients with diabetes and end-stage renal disease in Denmark. Diabetologia. 2007;50(5):922-9.

150. Pippias M, Jager KJ, Kramer A, Leivestad T, Sanchez MB, Caskey FJ, et al. The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry. Nephrol Dial Transplant. 2016;31(5):831-41.

151. Helve J, Haapio M, Groop PH, Gronhagen-Riska C, Finne P. Comorbidities and survival of patients with type 1 diabetes on renal replacement therapy. Diabetologia. 2011;54(7):1663-9.

152. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725-30.

153. Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. Diabetologia. 1985;28(8):590-6.

154. Tuomilehto J, Borch-Johnsen K, Molarius A, Forsen T, Rastenyte D, Sarti C, et al. Incidence of cardiovascular disease in Type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. Diabetologia. 1998;41(7):784-90.

155. Dahlquist G, Mustonen L. Analysis of 20 years of prospective registration of childhood onset diabetes time trends and birth cohort effects. Swedish Childhood Diabetes Study Group. Acta Paediatr. 2000;89(10):1231-7.

156. Rawshani A, Landin-Olsson M, Svensson AM, Nystrom L, Arnqvist HJ, Bolinder J, et al. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia. 2014;57(7):1375-81.

157. Borg H, Arnqvist HJ, Bjork E, Bolinder J, Eriksson JW, Nystrom L, et al. Evaluation of the new ADA and WHO criteria for classification of diabetes mellitus in young adult people (15-34 yrs) in the Diabetes Incidence Study in Sweden (DISS). Diabetologia. 2003;46(2):173-81.

158. Östman J, Lönnberg G, Arnqvist HJ, Blohme G, Bolinder J, Ekbom Schnell A, et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002. J Intern Med. 2008;263(4):386-94.

159. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. British journal of cancer. 2004;91(7):1229-35.

160. MacGregor MS. How common is early chronic kidney disease? A background paper prepared for the UK Consensus Conference on early chronic kidney disease. Nephrol Dial Transplant. 2007;22 Suppl 9:ix8-18.

161. Stengel B, Billon S, Van Dijk PC, Jager KJ, Dekker FW, Simpson K, et al. Trends in the incidence of renal replacement therapy for end-stage renal disease in Europe, 1990-1999. Nephrol Dial Transplant. 2003;18(9):1824-33.

162. Sorensen VR, Hansen PM, Heaf J, Feldt-Rasmussen B. Stabilized incidence of diabetic patients referred for renal replacement therapy in Denmark. Kidney Int. 2006;70(1):187-91.

163. Sjöblad S. Barn- och ungdomsdiabetes: ett vårdprogram. Lund, Sweden: Studentlitteratur; 1996.

164. Attvall S, Smith U. [Approved national guidelines for diabetic care. Diabetes Center, Sahlgrenska University Center, Gothenburg, Sweden]. Lakartidningen. 1999;96(38):3994-5.

165. Berne C, Agardh CD. [Diabetes mellitus--current Swedish national guidelines]. Nord Med. 1997;112(5):151-3, 75.

166. Costacou T, Fried L, Ellis D, Orchard TJ. Sex differences in the development of kidney disease in individuals with type 1 diabetes mellitus: a contemporary analysis. Am J Kidney Dis. 2011;58(4):565-73.

167. Muhlhauser I, Bender R, Bott U, Jorgens V, Grusser M, Wagener W, et al. Cigarette smoking and progression of retinopathy and

nephropathy in type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association. 1996;13(6):536-43.

168. Matuleviciene-Anangen V, Rosengren A, Svensson AM, Pivodic A, Gudbjornsdottir S, Wedel H, et al. Glycaemic control and excess risk of major coronary events in persons with type 1 diabetes. Heart. 2017;103(21):1687-95.

169. Ruggenenti P, Perna A, Zoccali C, Gherardi G, Benini R, Testa A, et al. Chronic proteinuric nephropathies. II. Outcomes and response to treatment in a prospective cohort of 352 patients: differences between women and men in relation to the ACE gene polymorphism. Gruppo Italiano di Studi Epidemologici in Nefrologia (Gisen). J Am Soc Nephrol. 2000;11(1):88-96.

170. Loikas D, Wettermark B, von Euler M, Bergman U, Schenck-Gustafsson K. Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden. BMJ open. 2013;3(5).

171. Svensson M, Nystrom L, Schon S, Dahlquist G. Age at onset of childhood-onset type 1 diabetes and the development of end-stage renal disease: a nationwide population-based study. Diabetes Care. 2006;29(3):538-42.

172. Dahlquist G, Rudberg S. The prevalence of microalbuminuria in diabetic children and adolescents and its relation to puberty. Acta paediatrica Scandinavica. 1987;76(5):795-800.

173. McKnight JA, Wild SH, Lamb MJ, Cooper MN, Jones TW, Davis EA, et al. Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabetic medicine : a journal of the British Diabetic Association. 2015;32(8):1036-50.

174. Nardi L, Zucchini S, D'Alberton F, Salardi S, Maltoni G, Bisacchi N, et al. Quality of life, psychological adjustment and metabolic control in youths with type 1 diabetes: a study with self- and parent-report questionnaires. Pediatric diabetes. 2008;9(5):496-503.

175. Hassan K, Heptulla RA. Glycemic control in pediatric type 1 diabetes: role of caregiver literacy. Pediatrics. 2010;125(5):e1104-8.

176. Davis CL, Delamater AM, Shaw KH, La Greca AM, Eidson MS, Perez-Rodriguez JE, et al. Parenting styles, regimen adherence, and glycemic control in 4- to 10-year-old children with diabetes. J Pediatr Psychol. 2001;26(2):123-9.

177. Wysocki T, Lochrie A, Antal H, Buckloh LM. Youth and parent knowledge and communication about major complications of type 1 diabetes: associations with diabetes outcomes. Diabetes Care. 2011;34(8):1701-5.

178. Hjern A. Chapter 7: children's and young people's health. Scand J Public Health Suppl. 2006;67:165-83.

179. Lewis KR, Clark C, Velarde MC. Socioeconomic factors associated with pediatric diabetic ketoacidosis admissions in Southern West Virginia. Clinical endocrinology. 2014;81(2):218-21.

180. Ward MM. Access to care and the incidence of end-stage renal disease due to diabetes. Diabetes Care. 2009;32(6):1032-6.

181. Carter PJ, Cutfield WS, Hofman PL, Gunn AJ, Wilson DA, Reed PW, et al. Ethnicity and social deprivation independently influence metabolic control in children with type 1 diabetes. Diabetologia. 2008;51(10):1835-42.

182. Robinson N, Lloyd CE, Stevens LK. Social deprivation and mortality in adults with diabetes mellitus. Diabetic medicine : a journal of the British Diabetic Association. 1998;15(3):205-12.

183. Persson S, Gerdtham UG, Steen Carlsson K, Swedish Childhood Diabetes Study G. Labor market consequences of childhood onset type 1 diabetes. Econ Hum Biol. 2016;23:180-92.

184. Persson S, Dahlquist G, Gerdtham UG, Steen Carlsson K, Swedish Childhood Diabetes Study G. Why childhood-onset type 1 diabetes impacts labour market outcomes: a mediation analysis. Diabetologia. 2018;61(2):342-53.

185. Goldman DP, Smith JP. Can patient self-management help explain the SES health gradient? Proc Natl Acad Sci U S A. 2002;99(16):10929-34.

186. Powell PW, Chen R, Kumar A, Streisand R, Holmes CS. Sociodemographic effects on biological, disease care, and diabetes knowledge factors in youth with type 1 diabetes. Journal of child health care : for professionals working with children in the hospital and community. 2012.

187. Walsh MG, Zgibor J, Songer T, Borch-Johnsen K, Orchard TJ. The socioeconomic correlates of global complication prevalence in type 1 diabetes (T1D): a multinational comparison. Diabetes Res Clin Pract. 2005;70(2):143-50.

188. Wysocki T, Harris MA, Wilkinson K, Sadler M, Mauras N, White NH. Self-management competence as a predictor of outcomes of intensive therapy or usual care in youth with type 1 diabetes. Diabetes Care. 2003;26(7):2043-7.

189. Holmstrom I, Halford C, Rosenqvist U. Swedish health care professionals' diverse understandings of diabetes care. Patient Educ Couns. 2003;51(1):53-8.

190. Onda Y, Nishimura R, Morimoto A, Sano H, Utsunomiya K, Tajima N, et al. Causes of death in patients with childhood-onset type 1 diabetes

receiving dialysis in Japan: Diabetes Epidemiology Research International (DERI) Mortality Study. J Diabetes Complications. 2015;29(7):903-7.

191. Zhang Y, Jarl J, Gerdtham UG. Are There Inequities in Treatment of End-Stage Renal Disease in Sweden? A Longitudinal Register-Based Study on Socioeconomic Status-Related Access to Kidney Transplantation. Int J Environ Res Public Health. 2017;14(2).

192. Zhang Y, Gerdtham UG, Rydell H, Jarl J. Socioeconomic Inequalities in the Kidney Transplantation Process: A Registry-Based Study in Sweden. Transplant Direct. 2018;4(2):e346.

193. Hommel K, Rasmussen S, Kamper AL, Madsen M. Regional and social inequalities in chronic renal replacement therapy in Denmark. Nephrol Dial Transplant. 2010;25(8):2624-32.