Clinical aspects of the relation between diabetes mellitus and kidney disease: From hyperfiltration to dialysis

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Contents

CHAPTER 1

General introduction

General Introduction

Diabetes mellitus (DM) is characterized by the body's inability to maintain adequate glucose levels, and the hallmark of its diagnosis are therefore increased levels of plasma glucose. Depending on the underlying pathophysiology, diabetes can be classified into different general categories. Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which pancreatic β-cells are destroyed over time and endogenous insulin production is lost. Type 2 (T2DM) diabetes is characterized by progressive loss of β cell insulin secretion, frequently accompanied by insulin resistance. Type 1 and 2 diabetes represent two broad categories, in which clinical presentation and disease progression may vary considerably and the distinction between the two types in clinical practice is not always clear-cut. Besides type 1 and type 2 DM, other etiologic subtypes such as monogenic diabetes (such as neonatal diabetes and maturity onset diabetes of the young (MODY)) have been discovered over the last decades.

The global prevalence of diabetes mellitus has increased dramatically over the past few decades. The total number of adults (20-79 years) with DM increased from 151 million in 2000 to 451 million in 2017[1]. This increase is mainly due to a in T2DM, which is, at least partially, thought to be secondary to the rise in metabolic syndrome and obesity. Between 1980 and 2013, the global prevalence of overweight and obesity combined rose by 27.5% for adults and 47.1% for children[2].

Patients with DM have an increased risk to develop microvascular and/or macrovascular complications due to hyperglycemia and common co-existing conditions such as hypertension and dyslipidemia. Complications, affecting the eyes (retinopathy), kidneys (nephropathy), and peripheral nervous system (neuropathy), are collectively called microvascular complications. Atherosclerotic cardiovascular disease such as coronary heart disease, cerebrovascular disease, or peripheral arterial disease are called macrovascular complications. The risk to develop complications depends on glycemic control, duration and type of DM[3, 4]. About 20-40 % of patients with DM develop chronic kidney disease (CKD)[5-7]. A substantial proportion of patients with DM will develop chronic kidney disease owing to their disease, but also associated conditions, such as hypertension and obesity will contribute. Patients with diabetes and CKD have an even further increased risk of adverse health care outcomes, higher risk of complications, comorbidities and use of polypharmacy and this imposes a huge economic burden on health care systems[8]. As major long-term consequences

of diabetes are the increased risk for cardiovascular, and renovascular disease, the overall management aims to reduce this cardiovascular risk. Furthermore, patients with DM have a reduced quality of life and life expectancy[9, 10].

Excess mortality in type 1 and type 2 DM is largely related to the presence of CKD. Among patients with T2DM younger than 55 years of age, and a normal or only slightly reduced estimated glomerular filtration rate (eGFR of ≥ 90 ml/min/ 1.73 m^2, or 60-90 ml/min/ 1.73 m^2) the excess risk of death from any cause is twice the risks among persons without diabetes. This risk further increases with decreasing kidney function; in DM patients with a clearly compromised renal function (eGFR of ≥ 15 -30 ml ml/ min/ 1.73 m^2), mortality risk is approximately 20 times higher[9]. In line, similar results are shown in patients with type 1 DM[10]**.** Consequently, preventing and management of CKD in patients with DM is a key aim of their overall management.

Pathophysiology of diabetic nephropathy

Kidney disease due to diabetes was first described in 1936 by Kimmelstiel and Wilson, who demonstrated characteristic nodular lesions in patients with diabetes, later termed nodular glomerulosclerosis[11]. Decades further, in the 1980's, it was demonstrated that diabetic kidney disease on average develops more than a decade after diabetes onset in patients with type 1 diabetes[12, 13]. In patients with newly diagnosed T2DM, about 7 % already have diabetic nephropathy at time of diagnosis, which is likely related to a long subclinical period of hyperglycemia; also comorbidities such as obesity and hypertension may play a role[14].

Diabetes related nephropathy is a progressive disease, the earliest sign being microalbuminuria (defined as urine albumin/creatinine ratio >30 mg/g), which can progress to macroalbuminuria (>300 mg/g) and a gradually decline in glomerular filtration rate, eventually leading to end stage renal disease (ESRD). Almost half of patients with established micro-albuminuria will progress to macro-albuminuria, which is associated with a ten foldhigher risk of progression to ESRD than patients with normoalbuminuria[15, 16]. Approximately 50 % of T2DM patients and 30 % of T1DM will develop CKD after 20 years of DM. CKD is defined by the presence of impaired renal function or elevated urinary albumin excretion or both (Table 1)[17-19].

Table 1. Clinical Criteria for the diagnosis of CKD[20]

Clinical Criteria for the diagnosis of CKD*
Estimated glomerular filtration rate of < 60 ml/min/ 1.73 m2
Urinary albumin/creatinine ratio of ≥ 30 mg/g (3 mg/mmol)
Urinary albumin excretion of ≥ 300 mg/g (30 mg/mmol) per 24 hours

*One or more of the following criteria must be present for more than 3 months and validated by repeated testing before a clinical diagnosis of chronic kidney disease can be made.

Many patients with type 1 and type 2 diabetes do not strictly follow this classic course of first developing micro-albuminuria, thereafter progression to macro-albuminuria and only thereafter a decline in eGFR. In the United Kingdom Prospective Diabetes Study (UKPDS) study, 28 % of patients with type 2 DM developed an estimated glomerular infiltration rate (eGFR) < 60 ml/min/ 1.73 m2 after a median of 15 years of follow-up; half of these patients did not show preceding albuminuria[21]. Also, in the Diabetes Control and Complications Trial (DCCT) study, 11 % of patients with type 1 DM developed an eGFR < 60 ml/min/ 1.73 m2 of which 40 % never had preceding albuminuria[22].

Different pathophysiologic pathways seem involved in the development of diabetic nephropathy. Hyperglycemia is essential in the development of diabetic nephropathy as kidney cells are unable to downregulate their glucose transporters in the setting of extracellular hyperglycemia and this subsequently results in an increase in their intracellular glucose concentration[23]. High intracellular glucose levels trigger pathogenic mediators such as reactive oxygen species and protein kinases which lead to cellular dysfunction, inflammation, apoptosis and fibrosis[24]. Although hyperglycemia is essential of the development of diabetic nephropathy, it is rarely the only contributor. Genetic factors influence onset and progression of kidney disease, as genome-wide association studies (GWAS) highlighted genetic variants associated with risk of CKD in large populations independent of actual glucose regulation[25]. Also environmental factors (e.g infections, heavy metals)[26], higher blood pressure[27-29], lipid abnormalities, (especially elevated triglycerides)[30, 31] and adiposity[32] contribute to diabetic nephropathy in type 1 DM as well as type 2 DM.

The "gold standard" for the diagnosis of diabetic nephropathy is a histopathology diagnosis. This invasive diagnostic procedure is however not routinely performed in clinical care settings because of a small risk related to this procedure (bleeding, haematuria) and often the lack of therapeutic consequences. Histopathologically, diabetic nephropathy can be categorized in four stages[33]. The first stage is characterized by isolated glomerular basement membrane thickening, the second phase by mesangial expansion in > 25 % of the total mesangium, the third phase is defined as nodular sclerosis, defined by at least one Kimmelstiel-Wilson lesion and less than 50 % diffuse global glomerulosclerosis and the fourth phase is defined as more than 50 % diffuse global glomerulosclerosis. The clinical relevance of knowing the exact stage in a patient is often limited; staging does not add predictive information regarding the progression of kidney failure, which is the case for other histopathological classifications for other renal diseases such as lupus nephritis[34].

Glycemic control and development of diabetic nephropathy

The importance of treatment of glycemic control in the development of CKD is illustrated by the DDCT/EDIC trial (1375 participants) in which improving glycemic control, reducing the HbA1c level of 9.1 % to 7.3 % in T1DM, lead to a reduction of progression to ESRD in 50 % of patients (16 compared to 8 events) and a slower decline in renal function (eGFR < 60 ml/min/ 1.73 m2 in 46 compared to 24 events) [35]. Moreover, pancreas transplantation in patients with type 1 DM is able to ameliorate the renal histopathological changes associated with diabetes, although this improvement is shown after at least 10 years of normoglycemia[36].

The ADVANCE trial (11,140 participants) showed that intensive glucose control (HbA1c target 6.5% or less) reduced the risk of ESRD in T2DM by 65% (20 compared to 7 events), microalbuminuria by 9% (1298 compared to 1410 patients), and macroalbuminuria by 30% (162 compared to 231 patients)[37]. Also the VDAT trial showed beneficial long term renal outcomes with intensive glycemic control[38]. Nevertheless, a substantial proportion of patients with DM still developed CKD. Furthermore "newer" glucose lowering agents have shown beneficial outcomes on cardiovascular and renal endpoints. Sodium glucose cotransporter-2 (SGLT2) inhibitors, working through inhibition of glucose reabsorption in the proximal kidney tubule and thereby lower plasma glucose levels, prevented the decline in GFR by about 40 % in patients with

type 2DM[39, 40]. Doubling of the serum creatinine level occurred after 2.6 years in 70 of 4645 patients (1.5%) in the empagliflozin (a SGLT2-inhibitor) group and in 60 of 2323 (2.6%) in the placebo group[41]. Mind however that the number needed to treat (that is, the number of patients to be treated to prevent one renal event such as creatinine doubling is substantial: around 100 patients need to be treated 2.9 years to prevent one diabetes related renal event. Several other effects than improvement in glucose control may contribute to renal and cardiovascular protection; lowering of blood pressure, decrease in intraglomerular pressure, reduction in albuminuria, and amelioration of volume overload are all plausible protective mechanisms[42-45]. Also glucagon like peptide receptor agonist (GLP-1ra), lowers plasma glucose levels. GLP-1ra enhances glucose-dependent insulin secretion, delay gastric emptying, and reduce postprandial glucagon secretion and food intake. GLP-1 ra, were associated with a lower risk of developing macro-albuminuria[46, 47]. Similar to the actions of SGLT2 inhibitors on the reno-cardiovascular system, it is likely that the beneficial effects of GLP-1 receptor agonists are also multifactorial, mediated by actions on body weight and blood pressure[48].

While the prevalence of DM (especially T2DM) is dramatically increasing, the incidence rates of ESRD due to diabetes declined from 2006 through 2012, and these rates remained stable in recent years[49]. This suggests improvement in care for patients with diabetes mellitus, which included not only improvement in glucose control, but also improvement in blood pressure treatment and lipid control, with an accompanying reduction in cardiovascular risk and associated mortality[50, 51].

End stage renal disease and diabetes mellitus

Diabetic nephropathy is the leading cause of end-stage-renal disease worldwide, although the majority of patients die from a cardiovascular event before reaching ESRD[52]. Diabetes as the primary cause of renal disease is responsible for 23% of the patients starting renal replacement therapy (RRT) in Europe and almost 50% in the USA[53, 54]. In patients with DM and ESRD the overall mortality risk is twofold higher than in non-diabetic patients with ESRD [55, 56]. In line, survival among dialysis patients with diabetes mellitus is inferior to survival of non-diabetic dialysis[57-59]. Patients with diabetic nephropathy have the largest number of co-morbid conditions within the ESRD population when compared with non-diabetic dialysis patients,

including retinopathy, foot disease including amputation, neuropathy, cognitive decline, mood disorders and cardiovascular disease[60]. The severity of co-morbid conditions and severity of CKD is strongly associated with adverse health related quality of life[61, 62].

Patients with DM have the highest mortality risk within the dialysis population. But this mortality risk might be different within the diabetes population with ESRD and be related to the severity of diabetic complications. It could be that mortality risk differs between patients with diabetes as a primary cause of ESRD and patients with diabetes as a co-morbid condition and a non-diabetic cause of ESRD. In that case a higher prevalence of diabetes related co-morbid conditions, could translate into an increased mortality risk.

Outline of this thesis

The overall aim of this thesis is to contribute to the understanding of the association between diabetes and several clinical aspects of chronic kidney disease.

In the first part of this thesis we describe the association between chronic kidney disease (CKD) and glucose metabolism. In **chapter 2** we estimate the prevalence of chronic kidney disease (CKD) among a Dutch sample of middle-aged adults and examine the association between glucose metabolism, obesity and chronic kidney disease (CKD). Furthermore, we examined the association between measures of glucose metabolism and measures of kidney function.

In the second part of this thesis we studied survival in patients with diabetes mellitus and ESRD. In **chapters 3 and 4** we compared survival in a dialysis population between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. Previous studies assessing survival made no distinction between patients with diabetes as primary renal disease and as a co-morbid condition. In patients with diabetic nephropathy, organ damage is likely not limited to the kidney but may also involve other organs resulting in retinopathy, neuropathy, diabetic foot disease and cardiovascular complications. In contrast, patients on dialysis with diabetes only as a co-morbid condition may have less pronounced organ damage. Therefore, we hypothesized that survival in patients on dialysis with diabetes as co-morbid condition may be better compared to patients with ESRD due to diabetic

nephropathy. In **chapter 3** we assessed and compared survival in a relatively small cohort of Dutch dialysis patients and in **chapter 4** we assessed and compared survival in a large sample of dialysis patients from 7 different European countries. In **chapter 5** we made a prediction model in order to predict 1-year mortality for diabetic incident dialysis patients. Survival among dialysis patients with diabetes mellitus is inferior to survival of non-diabetic dialysis patients and this might be related to the higher prevalence of diabetes related complications. Therefore, in **chapter 6** we assessed survival after amputation in diabetic patients compared to non-diabetic patients on dialysis. We hypothesized that these co-morbid conditions also contribute to a decreased survival in diabetic patients compared to non-diabetic patients on dialysis.

The results of the studies described in this thesis are summarized, discussed and put into clinical context in **chapters 7 and 8.**

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CHAPTER 2

The association of glucose metabolism and kidney function in middle-aged adults

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Abstract

Background

Previous clinical studies showed that various measures of glucose metabolism are associated with risk of chronic kidney disease in different populations, but results were not consistent in all aspects. In the present study we assessed measures of glucose metabolism and their association with kidney function in a population-based study. Furthermore, we studied glomerular hyperfiltration and micro-albuminuria because these are considered the earliest appearances of impaired kidney function in diabetes mellitus (DM).

Methods

The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort study of middle-aged men and women. We categorized the study population according to glycaemic levels into normoglycemia (reference group), pre-DM, known DM, and newly diagnosed DM. Outcome variables were serum creatinine, estimated glomerular filtration rate (eGFR), glomerular hyperfiltration and micro-albuminuria. We examined the association between measures of glucose metabolism (fasting glucose, HbA1c, fasting insulin, glucose area under the curve (AUC), insulin AUC, HOMA-IR, HOMA-B, Disposition index) and measures of kidney function. We performed linear regression for continuous outcomes and logistic regression analyses for binary outcomes (hyperfiltration or micro-albuminuria) adjusted for age, sex, BMI, blood pressure, smoking, antihypertensive agents and cardiovascular disease.

Results

Of the total population (N= 6338), 55 % participants were classified as normoglycemic (reference), 35 % as pre-diabetes, 7 % as diabetes mellitus, and 4 % as newly diagnosed diabetes mellitus. Clinically relevant chronic kidney disease (CKD-EPI <= 60 ml/min/ 1.73 m^2) was more frequent in pre-DM (3.5%), diagnosed DM (6.2%), and newly diagnosed DM (7.0%) compared to the reference group (1.2%). Presence of micro-albuminuria was more frequent in pre-DM (3.3%), diagnosed DM (6.3%), newly diagnosed DM (8.6%) than in normoglycemia (1.6 %). Compared to the reference group, diagnosed and newly diagnosed DM was associated with a slightly higher eGFR (+ 2.1 ml/min/ 1.73 m^2 (95% CI -0.2, 4.4) and + 2.7 ml/min/ 1.73 m^2 (95% CI -0.3, 5.7)) respectively. A 1% higher HbA1c was associated with an increased odds of

hyperfiltration: odds ratio 1.41 (95 % CI 1.06, 1.88). Higher levels of fasting plasma glucose, AUC glucose, and HOMA-B, were associated hyperfiltration. Fasting insulin, AUC insulin and HOMA-IR were not associated with hyperfiltration. Per mmol/l higher fasting glucose concentrations the odds ratio of micro-albuminuria was 1.21 (95 % CI 1.04, 1.42).

Conclusion

Both fasting and post-prandial glucose and HOMA-B, but not insulin resistance, were associated with glomerular hyperfiltration, while fasting glucose was also associated with micro-albuminuria. This implies that hyperinsulinemia as a measure of insulin resistance, is not associated with a first increase in eGFR (hyperfiltration) but is associated with a decline in eGFR.

Introduction

The global increase in obesity is a leading cause of the increased prevalence of pre-diabetes and type 2 diabetes mellitus (DM). 40% of patients with obesity has accompanying pre-diabetes[1], defined as a fasting glucose level of 100 to 125 mg/dL (5.6-6.9 mmol/L), or 2 hour plasma glucose of 140–199 mg/dL (7.8–11.0 mmol/L) after 75 mg oral glucose tolerance test, or HbA1c level of 5.7% to 6.4% (39-47 mmol/mol), according to the American Diabetes Association criteria[2]. Pre- diabetes is a clinically relevant condition as about 45-50 % of patients will develop type 2 DM within 10 years[3,4], and pre-diabetes is associated with a higher risk of macrovascular and microvascular complications, such as nephropathy[5-8]. Importantly, the risk of chronic kidney disease (CKD) is directly related to glucose levels: in US patients with normoglycemia the prevalence of CKD is 3 %, in patients with pre-diabetes 9 % and in patients with (un)diagnosed DM 14 %[9].

Postulated mechanisms by which pre-diabetes results in chronic kidney disease are an increase in glomerular hyperfiltration, vascular permeability and/or endothelial dysfunction and inflammation[10]. Previous studies showed that different measures of glucose metabolism (fasting glucose, HbA1c, fasting insulin, area under blood concentration curve (AUC), insulin AUC, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), HOMA of β-cell function (HOMA-B) and Disposition index) are associated with risk of chronic kidney disease. However, these studies were not in all aspects consistent. Some studies showed that elevated post-prandial measures of glucose metabolism might contribute more to chronic kidney disease than elevated fasting measures of glucose metabolism[11-16], while other studies showed the opposite[17-19]. However, none of the studies assessed so many different measures of glucose metabolism and their association with kidney function in a single large cohort. Moreover, these studies did not assess glomerular hyperfiltration as well as micro-albuminuria although this is considered the earliest appearances of impaired kidney function in DM and has been linked with an increased risk of diabetic nephropathy[17,20]. To date, it is unknown which measures of glucose metabolism are associated with both glomerular hyperfiltration as well as micro-albuminuria.

In the present study we examined the association between normoglycemia, pre-DM, DM, and newly diagnosed DM with chronic kidney disease, and markers thereof, among a Dutch cohort of middle-aged adults. Furthermore, we examined the

association between measures of glucose metabolism and earliest appearances of impaired kidney function, micro-albuminuria and glomerular hyperfiltration.

Methods

2.1 Study design and study population

The NEO study is a population-based, prospective cohort study designed to investigate pathways that lead to obesity-related diseases. The NEO study includes 6671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. The study design and population is described in detail elsewhere[21]. The present study is a cross-sectional analysis of the baseline measurements of the NEO study .

In short, men and women living in the greater area of Leiden (in the West of the Netherlands) were invited by letters sent by general practitioners and municipalities and by local advertisements. They were invited to respond if they were aged between 45 and 65 years and had a self-reported BMI of 27 kg/m^2 or higher. In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited to participate irrespective of their BMI, allowing a for a reference distribution of BMI in the general population.

After consecutive exclusion of participants with missing data on diabetes medication (N=64), fasting or post-prandial glucose (N= 245), fasting or post-prandial insulin (N=13), and HbA1c concentrations (N=11), 6338 participants were included in the present analyses.

The Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the design of the study. All participants gave their written informed consent.

2.2 Data collection

Participants were invited to a baseline visit at NEO study centre of the LUMC after an overnight fast. Prior to this study visit, participants collected urine (morning spot) and completed a general questionnaire at home to report demographic, lifestyle and clinical information. On the questionnaire, participants reported ethnicity by self-identification in eight categories which we grouped into Caucasian (reference) and

other. Tobacco smoking was reported in the three categories currently, formerly, and never smoking (reference). Highest level of education was reported in 10 categories according to the Dutch education system and grouped into high (including higher vocational school, university, and post-graduate education) versus low education (reference). Participants reported their medical history of diabetes and cardiovascular diseases. Pre-existing cardiovascular disease was defined as myocardial infarction, angina, congestive heart failure, stroke, or peripheral vascular disease. In addition, all use of medication in the month preceding the study visit was recorded. Family history of diabetes was reported as having any parent or sibling with diabetes or without DM (reference). Body weight was measured without shoes and one kilogram was subtracted from the body weight. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 min rest between consecutive measurements. The mean systolic, diastolic and mean arterial ([(2 _ diastolic blood pressure) + systolic blood pressure]/3) blood pressure were calculated.

2.3. Fasting glucose, insulin measurements and mixed meal test

Fasting blood samples were drawn from the antecubal vein after the participant had rested for 5 min. Within five minutes after the first blood sample, participants drank a liquid mixed meal. This meal (total 400 mL) contained 600 kCal, with 16 percent of energy (En%) derived from protein, 50 En% carbohydrates, and 34 En% fat. Subsequent blood samples were drawn 30 and 150 min after ingestion of the mixed meal. Fasting and post-prandial glucose and insulin concentrations were measured and from these Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), HOMA of β-cell function (HOMA-B) and Disposition index were calculated. In Supplementary Information S1, a detailed overview of laboratory methods and calculations is given.

We categorized the study population in four different groups, according to glycemic levels at baseline.

1. Normoglycemia (reference), defined as a fasting glucose level of < 5.6 mmol/l and a HbA1c level of < 5.7% (39 mmol/mol)

2. Pre-diabetes (pre-DM), defined as a fasting glucose level of 100 to 125 mg/dL (5.6-6.9 mmol/L) or HbA1c level of 5.7% to 6.4% (39-47 mmol/mol)

3. Diagnosed diabetes mellitus, defined as self- reported diabetes mellitus or use of glucose lowering medication.

4. Newly diagnosed diabetes mellitus, defined as no self-reported diabetes mellitus, no use of glucose lowering medication, but diabetes mellitus according to the ADA criteria with a fasting glucose level ≥ 126 mg/dL (≥7.0 mmol/L) or plasma glucose level ≥ 200 mg/dL (≥ 11.1 mmol/l) after mixed meal test or HbA1c level ≥ 6.5% (48 mmol/mol)[2].

2.4 Renal function and albuminuria

Serum creatinine (mg/dL) was used to calculate estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[22].

We defined glomerular hyperfiltration as an eGFR >90th percentile[17]. Urinary albumin was measured in an early-morning single urine void using an immunoturbidimetric assay and creatinine using a Jaffe kinetic compensated method between 1 September 2008 and 30 November 2010 and an enzymatic assay (IDMS calibrated against SRM 967) from 1 December 2010 until the end of the inclusion period. Because urinary creatinine concentrations are not affected by pseudochromogens they are exchangeable using either a Jaffe or an enzymatic method[23]. Micro-albuminuria was defined as urinary albumin/creatinine ratio of >= 2.5 mg/mmol in men and of >= 3.5 mg/mmol in women[22].

2.5 Statistical analyses

In the NEO study, individuals with a BMI > 27 kg/m^2 are overrepresented due to the sampling frame applied. To correctly represent baseline associations in the general population[24], adjustments for the oversampling of individuals with a BMI ≥ 27 kg/m^2 were made by weighting all participants towards the BMI distribution of participants from the Leiderdorp municipality[25], whose BMI distribution was similar to the BMI distribution of the general Dutch population[26]. All results were based on weighted analyses. As a consequence, all results apply to a population-based study without

oversampling of individuals with a BMI ≥ 27 kg/m^2. Because of the weighted analyses, percentages and proportions are given instead of absolute numbers of participants. Baseline characteristics are therefore expressed as mean (SD), or percentage, stratified by groups of glucose metabolism.

Our first study aim was to examine the association between categorized glucose levels (normoglycemia, pre-DM, DM and newly diagnosed DM) and chronic kidney disease, and markers thereof. Outcome variables studied were serum creatinine, eGFR (CKD-EPI), glomerular hyperfiltration and urinary albumin-creatinine ratio (UACR). A linear regression analysis was performed to calculate age- and sex-adjusted mean differences with 95% confidence intervals (95% CIs) in levels of serum creatinine, eGFR and albuminuria for the defined categories of glucose metabolism. The second study aim was to examine the associations between different measurements of glucose metabolism, (fasting glucose, HbA1c, fasting insulin, glucose AUC, insulin AUC, HOMA-IR, HOMA-B, Disposition index) and measures of kidney function. For this analysis we excluded 444 participants because of protocol violation during mixed meal test. We performed linear regression for continuous outcomes and logistic regression analyses for binary outcomes (hyperfiltration or micro-albuminuria). Participants who used oral glucose lowering medication and/or insulin (N=335) were excluded from the analyses where measures of glucose metabolism were used as independent variable. Analyses were adjusted for potential confounding due to age, sex, BMI, blood pressure, and smoking. In a sensitivity analysis we additionally adjusted for antihypertensive agents**,** heart failure, cerebrovascular accident and myocardial infarction, though for these variables, it may difficult to judge whether they act as a confounding factor or whether they are mediators for the glucose kidney function association. Analyses were performed using STATA (Statacorp, College Station, Texas, USA, version 14.0)

Results

3.1 Characteristics according to different glycemic categories

Of the total participants (N= 6338), 54.6 % participants were classified as normoglycemic (reference), 34.8 % as pre-diabetes, 6.9 % as diabetes mellitus and 3.8 % as newly diagnosed diabetes mellitus, shown in table 1. From the patients with known diabetes mellitus (DM), 58.9 % used oral glucose lowering medication, 4.6 % used insulin therapy,13.6 % patients used a combination of insulin and oral glucose lowering medication and 23.0 % used no glucose lowering medication. Mean age was highest in participants with diagnosed DM (59 years). BMI was lowest in participants with normoglycemia (BMI 25.4 kg/m^2) and highest in participants with diagnosed DM (30.8 kg/m^2). Presence of clinically relevant CKD, defined as eGFR <= 60 ml/min/ 1.73 m^2, was higher in participants with pre-DM (3.5 %), DM (6.2 %) and newly diagnosed DM (7.0 %) than in the reference group (1.2 %). Also, presence of micro-albuminuria was higher in participants with pre-DM (3.3 %), DM (6.3 %), newly diagnosed DM (8.6 %) than in the reference group (1.6 %). More participants with pre-DM used angiotensin converting enzyme inhibitors or angiotensin receptor blockers and statins compared with the participants with normoglycemia. Fasting and post-prandial measures of glucose metabolism according to glycemic catagories are provided in table 2.

Table 1. Characteristics of the study population of the Netherlands Epidemiology of Obesity study*.

	Normoglycemia (reference)	Pre-DM	DM	Newly diagnosed DM
Proportion of participants (%)	54.6	34.8	6.9	3.8
Age (y)	54.9 (5.4)	57.4 (6.4)	58.5 (7.3)	57.6 (6.8)
Sex (% men)	38	57	53	64
BMI (kg/m2)	25.4 (3.5)	27.8 (5.2)	30.8 (8.0)	29.7 (7.0)
Blood pressure (mmHg)				
systolic	128.1 (15.0)	134.2(19.3)	135.7 (23.5)	137.2 (21.1)
diastolic	82.3 (9.1)	84.7 (11.9)	84.8 (13.4)	88.1 (12.8)
Tobacco smoking (% never)	41	35	25	29
Ethnicity (% Caucasian)	95	95	90	94
Waist circumference (cm)	89.0 (11.0)	97.5 (14.3)	106.2 (19.1)	103.3 (17.1)
Hip circumference (cm)	102.3 (7.5)	106.0 (10.5)	109.8 (17.1)	108.7 (13.6)
Use of ACEi/ARB (% yes)	10	18	52	23
Statin use (% yes)	6	13	71	19
Family history of diabetes (% yes)	25	34	57	41
Comorbidity				
Heart failure (%)	0.4	0.4	1.3	0.8
Cerebrovascular disease (%)	1.4	2.4	7.8	1.0
Cardiovascular disease* (%)	1.2	2.0	6.7	4.0

	Normoglycemia (reference)	Pre-DM	DM	Newly diagnosed DM
Biomarkers				
Serum creatinine (umol/ll)	75.6 (12.0)	79.3 (18.1)	75.7 (25.1)	78.3 (19.6)
CKD-EPI (ml/min/1.73 m2)	86.6 (10.7)	85.0 (14.7)	86.9 (20.7)	86.7 (18.7)
Urine (morning spot)				
albumin/ creat ratio (mg/mmol)	0.7 (2.5)	1.1 (6.8)	2.6 (21.5)	2.0 (17.4)
micro- albuminuria (% yes)	1.6	3.3	6.3	8.6
Total cholesterol (mmol/L)	5.7 (0.9)	5.8(1.2)	4.7 (1.4)	5.7 (1.6)
HDL (mmol/L)	1.6 (0.4)	1.5 (0.5)	1.3 (0.5)	1.3 (0.5)
LDL (mmol/L)	3.5 (0.8)	3.7 (1.1)	2.7 (1.2)	3.5 (1.4)
Triglycerides (mmol/L)	1.1 (0.7)	1.5 (1.1)	1.6 (1.4)	1.8 (1.4)
ALT (U/l)	24 (11)	28 (15)	31 (22)	34 (23)
AST (U/l)	24 (8)	25 (9)	26 (14)	27 (15)
Hb (mmol/l)	8.6 (0.9)	8.9 (1.0)	8.7 (1.0)	9.3(0.8)
CRP (mg/L)	1.9 (2.4)	2.4 (3.6)	3.0 (5.1)	3.6 (4.7)

* Results were weighted toward the BMI distribution of the general population (n= 6338). Data are expressed as %, mean (standard deviation).

DM; diabetes mellitus, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, HDL; high density lipoprotein, LDL; low density lipoprotein. Cardiovascular disease was defined as myocardial infarction.

Table 2. Glucose metabolism in participants with normoglycemia, pre-DM, diagnosed DM and newly diagnosed DM*.

	Normoglycemia DM	Pre-DM	Diagnosed DM	Newly diagnosed
Fasting glucose (mmol/l)	5.1 (0.3)	6.0 (0.4)	8.0 (3.0)	7.9 (2.7)
HbA1c (%)	5.2 (0.2)	5.4 (0.3)	6.7 (1.6)	6.2 (1.5)
Fasting insulin (mU/l)	8.0 (4.9)	12.0 (8.4)	17.7 (28.7)	18.5 (23.6)
Glucose *AUC*	5.5 (0.8)	6.8 (1.1)	10.6 (4.5)	9.8 (3.9)
Insulin *AUC*	44.0 (23.5)	57.9 (38.0)	55.6 (49.3)	72.7 (58.4)
HOMA-IR	1.8 (1.1)	3.2 (2.3)	6.6 (13.7)	6.4 (8.4)
HOMA-B	104.0 (62.2)	98.3 (66.9)	91.0 (124.8)	92.8 (111.9)
Disposition index	51.8 (38.4)	30.6 (11.7)	14.1 (11.8)	16.6 (12.9

* Results were weighted toward the BMI distribution of the general population (N= 5894) 444 participants were excluded because of protocol violation during mixed meal test. Data are shown as mean (standard deviation).

3.2 Associations between different glycemic catagories and measures of kidney function

Table 3 shows the adjusted mean difference in eGFR between the four glycaemic categories. eGFR was similar in participants with normoglycemia and pre-DM. Diagnosed and newly diagnosed DM was associated with a higher eGFR, respectively + 2.1 ml/min/ 1.73 m^2 (95% CI -0.2, 4.4) and + 2.7 ml/min/ 1.73 m^2 (95% CI -0.3, 5.7). Pre-DM and (newly) diagnosed DM were associated with increased micro-albuminuria (table 4). The odds ratio for micro-albuminuria was 1.6 (95% CI 0.9, 2.7) in participants with pre-DM and 2.8 (95% CI 1.5, 5.4) in participants with newly diagnosed DM compared with normoglycemia.

Table 3. Mean difference CKD-EPI in patients with pre-DM, diagnosed DM, newly diagnosed DM, compared with normoglycemia*.

	Normoglycemia (reference)	Pre-diabetes	Diagnosed DM	Newly diagnosed DM
Model a	86.3	0.0 (-0.9, 1.0)	2.1 (0.0, 4.2)	2.6 (-0.3, 5.5)
Model b	86.3	0.1 (-0.9, 1.1)	2.2 (-0.1, 4.4)	2.7 (-0.2, 5.7)
Model c	86.3	-0.1 (-1.1, 0.9)	2.2 (-0.0, 4.5)	2.7 (-0.3, 5.6)
Model d	86.3	-0.1 (-1.1, 0.9)	2.1 (-0.2, 4.4)	2.7 (-0.3, 5.7)

* Results were weighted toward the BMI distribution of the general population (N= 5879). 444 participants were excluded because of protocol violation during mixed meal test.

- Model a adjusted for age and sex
- Model b additionally adjusted for BMI
- Model c additionally adjusted blood pressure, smoking, antihypertensive agents
- Model d additionally adjusted heart failure, cerebrovascular accident and myocardial infarction

Table 4. Odds ratio's of micro- albuminuria in patients with pre-DM, diagnosed DM, newly diagnosed DM compared to normoglycemia*.

	Normoglycemia (reference)	Pre-diabetes	Diagnosed DM	Newly diagnosed DM
Model a	1.0	2.2 (1.3, 3.6)	3.8 (2.2, 6.8)	5.3 (2.8, 10.3)
Model b	1.0	1.7 (1.0, 2.8)	2.1 (1.3, 3.7)	3.4 (1.8, 6.5)
Model c	1.0	1.6 (0.9, 2.6)	1.6 (1.0, 2.8))	2.8 (1.5, 5.4)
Model d	1.0	1.5 (0.9, 2.6))	1.6 (0.9, 2.7)	2.8 (1.5, 5.4)

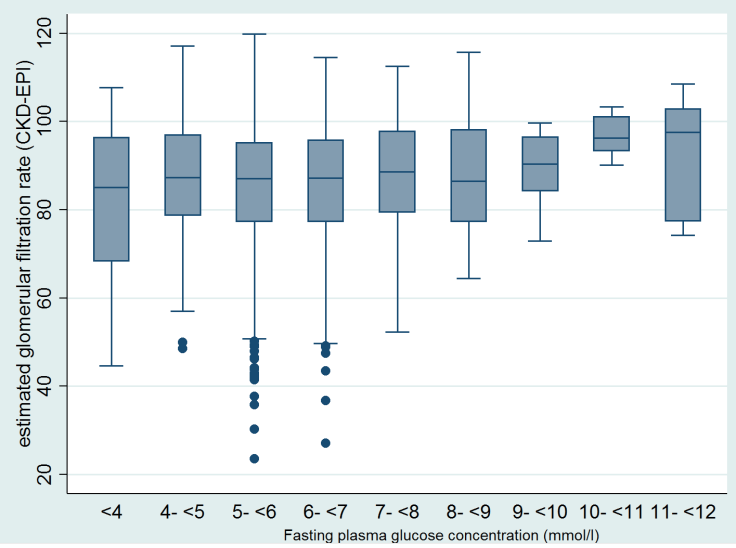
* Results were weighted toward the BMI distribution of the general population (N=5870). 444 participants were excluded because of protocol violation during mixed meal test.

- Model a adjusted for age and sex
- Model b additionally adjusted for BMI
- Model c additionally adjusted blood pressure, smoking, antihypertensive agents
- Model d additionally adjusted heart failure, cerebrovascular accident and myocardial infarction

3.3 Associations of different measures of glucose metabolism, hyperfiltration and micro-albuminuria in the total study population.

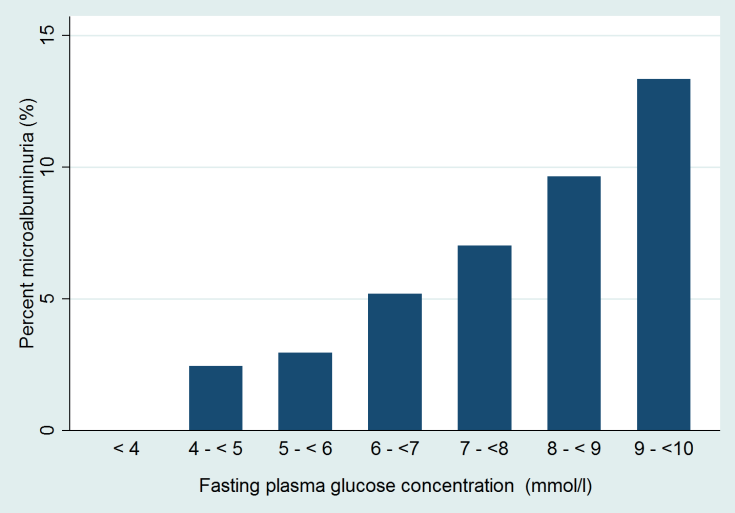
Higher fasting glucose concentrations were associated with higher eGFR (figure 1A). Micro-albuminuria was associated with higher fasting glucose levels: micro-albuminuria was not seen in fasting glucose levels < 4 mmol/L, while in participants with fasting glucose levels between 9 and below 10 mmol/L the percentage was almost 14 % (figure 1B).

Figure 1A. Association between fasting plasma glucose and eGFR.



Results were weighted toward the BMI distribution of the general population (N=6003). Patients using glucose lowering drugs were excluded.

Figure 1B. Association between fasting plasma glucose and micro-albuminuria.



* Results were weighted toward the BMI distribution of the general population (N=6003). Patients using glucose lowering drugs were excluded. Micro-albuminuria was defined as urinary albumin/creatinine ratio of >= 2.5 mg/mmol in men and of >= 3.5 mg/mmol in women.

We examined the associations between different measures of glucose metabolism, hyperfiltration and micro-albuminuria (see table 5). A 1% higher HbA1c level was associated with an odds ratio for hyperfiltration of 1.41 (95 % CI 1.06, 1.88). Also, higher levels of fasting plasma glucose, AUC glucose, and HOMA-B were associated with increased odds ratio's of hyperfiltration (table 5). Hyperinsulinemia, as a measure of insulin resistance, was not associated with hyperfiltration. Data were similar if we included participants who used oral glucose lowering medication and/or insulin (data not shown). Both fasting plasma glucose and HbA1c were associated with micro-albuminuria (table 5).

Table 5. Association of different measures of glucose metabolism with hyperfiltration and micro-albuminuria.

Measures of glucose metabolism	Odds ratio (95 % CI) for hyperfiltration	Odds ratio (95 % CI) for micro-albuminuria
Fasting glucose		
- per mmol/L (18 mg/dL)	1.27 (1.11, 1.46)	1.21 (1.04, 1.42)
HbA1c		
- per % unit	1.41 (1.05, 1.87)	1.36 (1.00, 1.86)
Fasting insulin		
- per mU/l	0.99 (0.97, 1.01)	1.01 (1.00, 1.03)
AUC glucose		
- per unit	1.22 (1.11, 1.34)	1.11 (0.97, 1.26)
AUC insulin		
- per unit	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
HOMA-IR		
- per unit	1.00 (0.94, 1.05)	1.05 (0.97, 1.14)
HOMA-1B		
- per unit	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)
IDI-isi		
- per unit	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)

* Results were weighted toward the BMI distribution of the general population (N=5572). Patients using glucose lowering drugs were excluded. Logistic regression analysis with hyperfiltration and micro-albuminuria as the dependent variable. All models were adjusted for age, sex, weight, diastolic and systolic BP smoking, and the use of ACE inhibitors or ARB.

Discussion

In this large cross-sectional study of middle-aged men and women we observed a relatively low proportion of patients with chronic kidney disease. Furthermore we found that both fasting and post-prandial glucose and HOMA-B, but not insulin resistance, were associated with glomerular hyperfiltration, while fasting glucose was also associated with micro-albuminuria.

As expected, our study showed that patients with chronic kidney disease had higher glucose levels compared to patients without CKD. Also, we demonstrated that the proportion of patients with kidney disease in this Dutch study is much lower than in previous studies[9,13]. This relatively low proportion of patients with chronic kidney disease might be explained by a relatively good metabolic control in our study as

illustrated by a good glycemic, blood pressure and lipid control. Furthermore, it might also be related to different study populations. First, in a US study[9], many patients had no insurance (8.9 %-19.4 %) while in the Netherlands all patients have basic insurance and patients with an insurance have better health care outcomes[27]. Second, mean BMI is higher in the United States than in the Netherlands and BMI is a strong risk factor of chronic kidney disease[28]. Third, almost all our participants had a non-hispanic caucasian ethnicity, which might contribute to the lower prevalence of CKD, as the prevalence of CKD in a non-caucasian population is higher[29].

Previous cohort studies showed conflicting results whether pre-DM is associated with chronic kidney disease. Some studies showed a positive association between pre-diabetes and chronic kidney disease, as in a higher prevalence of glomerular hyperfiltration and albuminuria compared to participants without DM [11,30,31]. Other longitudinal studies showed that pre-diabetes was not an independent risk factor for chronic kidney disease[13,32]. However, information on micro-albuminuria was not available in these studies, meaning that this early sign of kidney damage may had been missed. We showed in participants with pre-DM that eGFR was similar to participants with normoglycemia, but the odds of micro-albuminuria was 1.7 (95 % CI 1.0, 2.8) times higher. However, after adjustment for vascular risk factors the odds ratio was attenuated (OR 1.5 (95 % CI 0.9, 2.7) suggest that concomitant vascular disease risk factors explain most of the increased odds of development of micro-albuminuria in pre-DM.

The observed higher eGFR in patients with (newly) diagnosed DM is in line with other studies [11,33,34]. In our study, patients with diagnosed DM, although not recently diagnosed, had a relatively "mild" diabetes mellitus. This was reflected by good glycemic control, a small number of patients with insulin use and a low prevalence of diabetic complications. These characteristics might explain the observed higher eGFR, reflecting glomerular hyperfiltration, instead of a decline in eGFR.

Glomerular hyperfiltration is considered as an early manifestation of diabetic kidney nephropathy and may contribute to nephropathy progression and GFR decline[20,35,36]. However a recent study in patients with type 1DM showed that early hyperfiltration was not associated with a higher long-term risk of decreased GFR, defined as an eGFR < 60 ml/min per 1.73 m^2[37]. A potential limitation of that study was that hyperfiltration was assessed at baseline (median 4 years after diagnosis)

and not during long term follow up (median 28 years). Furthermore, glucose control was not optimal (mean HbA1c 8.8 %). A reason for the negative result of that study, which showed that hyperfiltration was not associated with a higher long-term risk of decreased GFR, might be that glomerular hyperfiltration is (partially) reversible after improvement of glucose control.

In our study, we evaluated different measures of glucose metabolism, and showed that both fasting and post-prandial glucose levels and HOMA-B were associated with glomerular hyperfiltration, while only fasting glucose was associated with micro-albuminuria. Our results showed no association between insulin resistance with glomerular hyperfiltration and micro-albuminuria. These results are in line with another study which reported that impaired fasting glucose was associated with glomerular hyperfiltration, whereas hyperinsulinemia was not[17]. Our results add to the hypothesis that hyperinsulinemia as a measure of insulin resistance, is not associated with a first increase in eGFR (hyperfiltration) but is associated with a decline in eGFR. This might be explained by direct kidney damage, by mechanisms such as inflammatory cytokines and lipotoxicity[38-40]. Other studies reported that insulin resistance in a non-diabetic population contributes to progressive CKD[41,42, but hyperfiltration was not assessed in these studies. Our study also showed that hyperinsulinemia was not associated with micro-albuminuria. This is line with another study[43] but in contrast with other reports[44,45]. However, these studies were performed in a different study population (mainly non-caucasian) and furthermore no adjustments were made for the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

This study adds new knowledge to existing literature. First, the proportion of patients with kidney disease in this Dutch study cohort with a good metabolic control was relatively low. Second, we showed that insulin resistance was not associated with glomerular hyperfiltration and micro-albuminuria. The strengths of this study are the evaluation of kidney function by eGFR, as well as glomerular hyperfiltration and micro-albuminuria. Micro-albuminuria is a known risk factor for the development of kidney disease in the setting of diabetes [46,47]. Furthermore, the NEO population consisted of a large study population and included an extensive set of measures of glucose metabolism, including a mixed meal test. This made it possible to evaluate the associations of many different measures of glucose metabolism with measures of kidney function in one large patient cohort.

Our study also has a number of limitations that need to be considered. The cross-sectional design limits inferences on causality. Further we did not perform a glucose tolerance test, but a mixed meal test and measured post-prandial glucose levels at 30 and 150 min. A two-hour glucose value was not obtained and therefore impaired glucose tolerance could not be assessed. However, we combined fasting glucose, HbA1c levels, elevated post-prandial levels (≥ 11.1 mmol/l) and used accepted definitions of pre-diabetes[2]. Another limitation is the use of estimated GFR, although the CKD-EPI formula has proven to be more accurate compared with the MDRD formula, it has not been validated above 90 ml/min/1.73m^2 and might underestimate hyperfiltration in obesity[48]. Isotope clearance measurements are the gold standard but are seldom used in large epidemiological studies due to time, high cost and invasiveness. Further there is no consensus about the definition of hyperfiltration. Some studies referred to hyperfiltration as a GFR exceeding the upper limit of normal range (eGFR > 90th percentile) or a measured GFR > 120 ml/min/1.73m^2[17,34,35]. Another limitation is the lack of confirmation of micro-albuminuria in a second urine portion. Although patients delivered a morning urine sample, which reduces the number of false positives, we cannot exclude that some patients had transient micro-albuminuria.

Further follow up studies are needed to investigate whether patients with pre-DM or DM and hyperfiltration are at risk of further progression of kidney disease. If future studies confirm that patients with glomerular hyperfiltration have a high risk of further progression of kidney disease, this will also give the opportunity for early intervention in diminishing renal disease progression, by modulating intraglomerular pressure with sodium-glucose cotransporter-2 inhibitors and renin-angiotensin-aldosteron system inhibitors.

In conclusion, in contrast with other studies, the proportion of patients with kidney disease in this Dutch study population was relatively low, which might be related to good metabolic control. Furthermore, we showed that both fasting and post-prandial glucose and HOMA-B, but not insulin resistance, were associated with glomerular hyperfiltration, while fasting glucose was also associated with micro-albuminuria. This implies that hyperinsulinemia as a measure of insulin resistance, is not associated with a first increase in eGFR (hyperfiltration) but is associated with a decline in eGFR. The results need further confirmation in cohorts with long term follow up.

Supplementary Information S1

Laboratory methods and calculations

Fasting plasma glucose concentrations were determined by enzymatic and colorimetric methods (Roche Modular Analytics P800, Roche Diagnostics, Mannheim, Germany; CV < 5%) and serum insulin concentrations were determined by an immunometric method (Siemens Immulite 2500, Siemens Healthcare Diagnostics, Breda, The Netherlands; CV < 5%). HbA1c concentrations were measured by HPLC boronate affinity chromatography (Primus Ultra, Siemens Healthcare Diagnostics, Breda, The Netherlands; CV < 3%). All analyses were performed in the central clinical chemistry laboratory of the LUMC (4). From measured glucose and insulin concentrations, we calculated Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and HOMA of beta-cell function (HOMA-B) as markers of hepatic insulin resistance and steady-state insulin secretion (5). HOMA-IR was calculated as fasting insulin (μU/ml) * fasting glucose (mmol/l) / 22.5 and HOMA-%B as 20 * fasting insulin (μU/ml) / fasting glucose (mmol/l) − 3.5 (5;6). In addition, we calculated the total area under the curve for overall glucose ($glucose_{AUC}$) and insulin ($insulin_{AUC}$) concentrations by the trapezoidal rule as (15 * fasting concentration + 75 * $concentration_{30min}$ + 60 * $concentration_{150min}$) / 150. The Disposition Index a marker of whole-body beta-cell function that accounts for variations in whole-body insulin sensitivity, was calculated as Insulinogenic Index * Matsuda Insulin Sensitivity Index (7). Insulinogenic Index was calculated as total $insulin_{AUC}$ / total $glucose_{AUC}$ and Matsuda Insulin Sensitivity Index as 10,000/square root [fasting glucose (mg/dl) * fasting insulin (μU/ml)] * [$mean_{glucose0\text{-}150}$ * $mean_{insulin0\text{-}150}$] (7-9)

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CHAPTER 3

Survival in dialysis patients is not different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition

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Abstract

Background

On dialysis, survival among patients with diabetes mellitus is inferior to survival of non-diabetic patients. We hypothesized that patients with diabetes as primary renal disease have worse survival compared to patients with diabetes as a co-morbid condition and aimed to compare all-cause mortality between these patient groups.

Methods

Data were collected from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter, prospective cohort study in which new patients with end stage renal disease (ESRD) were monitored until transplantation or death. Patients with diabetes as primary cause of ESRD were compared with patients with diabetes as co-morbid condition and both of these patient groups were compared to patients without diabetes. Analysis was performed using Kaplan-Meier and Cox regression.

Results

Fifteen % of the patients had diabetic nephropathy as primary renal disease (N=281); 6 % had diabetes as co-morbid condition (N=107) and 79 % had no diabetes (N=1465). During follow-up 42 % of patients (N=787) died. Compared to non-diabetic patients, mortality risk was increased for both patients with diabetes as primary renal disease HR: 1.9 (95 % CI 1.6, 2.3) and for patients with diabetes as co-morbid condition HR: 1.7 (95 % CI 1.3, 2.2). Mortality was not significantly higher in patients with diabetes as primary renal disease compared to patients with diabetes as co-morbid condition (HR 1.06; 95 % CI 0.79, 1.43).

Conclusions

This study in patients with ESRD showed no survival difference between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. Both conditions were associated with increased mortality risk compared to non-diabetic patients.

Background

Diabetes mellitus is a major contributor to the development of renal failure[1-3]. The proportion of patients with diabetes mellitus that progresses to End Stage Renal Disease (ESRD) is increasing. The increased prevalence of diabetes mellitus is estimated to account for 28 % of the increased incidence of renal replacement therapy (RRT) in general[4,5]. A marked difference exists in incidence of patients with ESRD due to diabetic nephropathy between Europe and the United States. The percentage of patients entering RRT because of diabetic nephropathy is 10-15 %[5] in Europe compared to 45 % in the United States[6].

Survival of diabetic patients and non- diabetic patients with ESRD has improved in the past 10 years[5,7,8]. However, survival among diabetic dialysis patients remains inferior to that of non- diabetic patients[2,9]. Patients with diabetic nephropathy have the largest number of co-morbid conditions within the ESRD population[4]. These conditions are mainly vascular in nature[9-11]. One can hypothesize that in patients with diabetic nephropathy organ damage is not limited to the kidney but also involves other organs resulting in retinopathy, neuropathy and cardiovascular complications. In contrast, patients on dialysis with diabetes as a co-morbid condition may have less pronounced organ damage. Therefore, survival in patients on dialysis with diabetes as co-morbid condition may be better compared to patients with ESRD due to diabetic nephropathy. However, at present this is unknown.

The aim of our present study was therefore to compare survival of dialysis patients with diabetes mellitus as primary cause of the renal failure with dialysis patients with diabetes mellitus as co-morbid condition. Mortality rates in these two groups were compared to mortality rates in dialysis patients without diabetes mellitus. Because of the high incidence of cardiovascular morbidity and mortality in the dialysis population, especially in patients with diabetes, cardiovascular mortality was compared between the three groups. In addition, we performed a stratified analysis according to treatment modality.

Methods

Patient selection

Patients who were ≥18 years and who began chronic dialysis as the initial renal replacement therapy were eligible for this study. Three months after the start of dialysis was considered as the baseline of present analyses. Informed consent was obtained before inclusion. This study was approved by the Medical Ethics Committees of all participating centres.

Design

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a multicenter, prospective cohort study in 38 dialysis centres throughout the Netherlands. New patients with ESRD were included at the time of initiation of dialysis treatment, from January 1, 1997 and were monitored at 3, 6 and thereafter at 6 month intervals until renal transplantation, death or January 1, 2007. Data on demographic characteristics, co-morbidities and primary kidney disease were collected at the time of entry into the study. Dialysis characteristics were collected 3 months after the start of RRT and at 6 month intervals thereafter. At the 3 month visit (baseline) patients were classified according to the treatment modality, i.e. peritoneal dialysis (PD) or hemodialysis (HD). The type and cause of renal disease and causes of death were defined according to the criteria of the European Renal Association- Dialysis and Transplantation Association[12].

Diabetes mellitus

For the present analysis patients were categorized as follows: 1. patients with diabetic nephropathy as the primary cause of ESRD (diabetes glomerulosclerosis or diabetic nephropathy, type 1 and type 2)[10] and 2. patients with diabetes mellitus as a co-morbid condition, but without diabetic nephropathy as a primary cause of ESRD, and 3. patients with ESRD without diabetes mellitus.

Study endpoints

The primary endpoint of the present analysis was all cause mortality. Cardiovascular mortality rates were calculated. Cardiovascular mortality was defined as death attributed to myocardial ischemia and infarction, heart failure, cardiac arrest, and cause of death uncertain/ not determined[13]. Cause of death uncertain/ not determined was considered as cardiovascular death because most of these patients died of a sudden death syndrome and this syndrome had a cardiovascular origin.

Statistical analysis

Mortality was calculated as incidence rate and expressed as number of deaths/ 1000 person years. Time to event analysis was performed using Kaplan Meier analysis and the Cox proportional hazard's model. Hazard ratios (HR) were calculated for comparison of all-cause and cardiovascular mortality in the 3 groups. All registered deaths during the follow up period were allocated to treatment modality at the 3 month visit, ignoring modality switches (intention to treat analysis). The multivariate Cox proportional hazards model was extended with adjustments for the possible confounding effects of age and gender. Other clinical characteristics at baseline (such as hypertension, cardiovascular disease) were considered to be potential consequences of diabetes, and thus not used as confounders in multivariate analyses [14]. In an additional analysis the effects of treatment modality (peritoneal dialysis versus hemodialysis) on mortality were studied. All analyses were performed with SPSS statistical software, version 14.0.

Results

Patient characteristics

Between January 1997 and January 2007, 1853 patients who survived the first 3 months of dialysis were included. Fifteen percent of patients had diabetes mellitus as primary renal disease, 6% of patients had diabetes as a co-morbid condition whereas the majority of the cohort (79 %) had a renal disease without diabetes (Table 1). Patients with diabetes as co-morbid condition were older at baseline (median age 69, range 28-86 y) compared to patients with diabetes as primary renal disease (63,

28-84 y) and patients without diabetes (62, 18-92 y). Retinopathy for which laser coagulation therapy was performed was more frequent in patients with diabetes as primary renal disease compared to patients with diabetes as a co-morbid condition (62 % versus 11 %). During follow-up 33 % of the patients without diabetes received a renal transplant compared to 17 % of the patients with diabetes as primary renal disease and 8 % of the patients with diabetes as a co-morbid condition.

Table 1. Baseline characteristics at 3 months after the start of dialysis.

	Diabetes as primary renal disease	**Diabetes as co-morbid condition**	**Without diabetes**	**P value***
	N=281	**N=107**	**N=1465**	
Age (median yr)	63 (28 -84)	69 (28-86)	62 (18-92)	0.00
Male gender (%)	54	58	64	0.01
Primary renal disease (%)				
Diabetes Mellitus	100	0	0	
Glomerulonephritis	0	22	24	
Renal Vascular disease	0	22	19	
All other	0	56	58	
Modality of dialysis (%)				
HD	64	75	62	0.03
Comorbidity (%)				
Myocardial infarction	14	30	11	0.00
Cerebrovascular disease	15	9	7	0.00
Peripheral vascular disease	23	26	12	0.00
Retinopathy (lasercoagulation) (%)	62	11	0	
Medication: (%)				
antihypertensive agents	89	79	82	0.01
ACEi, ARBs	36	28	21	0.36
Use of insulin s.c.(%)	75	36	0	
Blood pressure (mean, mm Hg)				
Systolic	154 (90-260)	151 (100-210)	148 (90-234)	0.00
Diastolic	79 (44-120)	80 (54-115)	84 (44-145)	0.00

	Diabetes as primary renal disease N=281	Diabetes as co-morbid condition N=107	Without diabetes N=1465	P value*
Smoking (%)	14	23	24	0.01
Body Mass Index (kg/m2)	27 (16- 44)	26 (16-45)	25 (15-56)	0.00
Haemoglobin (g/dl)	11 (6-16)	11 (6-14)	11 (6-23)	0.11
Albumin (mmol/l)	34 (14-47)	35 (13-46)	36 (14-67)	0.02
Residual GFR (ml/min)	6	6	5	0.06

*p-value: for continuous variables we used Anova analysis and for binary analysis we used Chi-Square analysis.

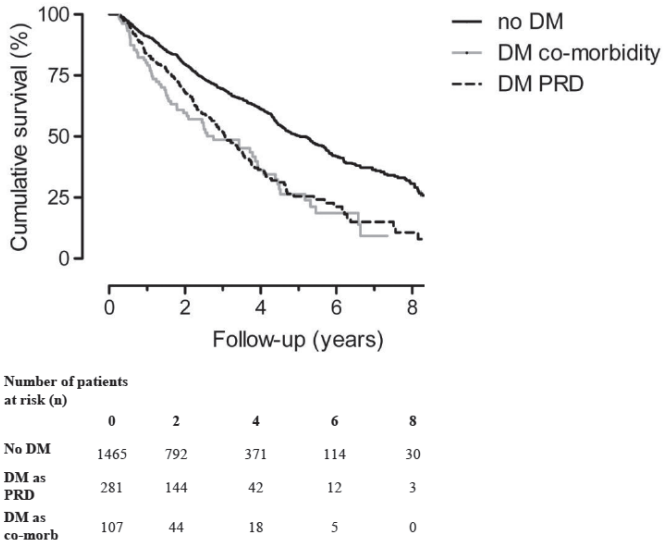
Mortality

During follow up, 787 patients (42 %) of the total group died. The overall mortality rates and cardiovascular mortality rates for each patient group are shown in table 2. Mortality was higher in patients with diabetes as primary renal disease (HR 1.9; 95 % CI 1.6, 2.2) and in those with diabetes as a co-morbid condition (2.1, 95 % CI 1.6, 2.7) compared to patients without diabetes (Figure 1). After adjustment for age and gender, the HR for patients with diabetes as primary renal disease was 1.9 (95 % CI 1.6, 2.3) and 1.7 (95 % CI 1.3, 2.2) for patients with diabetes as a co-morbid condition, as compared to non-diabetic patients**.** Further adjustment for smoking, blood pressure, body mass index, serum albumin, myocardial infarction or stroke, the HR for patients with diabetes as primary renal disease was 1.8 (95 % CI 1.3, 2.4) and 1.8 (95 % CI 1.5, 2.3) for patients with diabetes as a co-morbid condition, as compared to non-diabetic patients**.** Also mortality in patients with diabetes as primary renal disease was not clearly higher compared to patients with diabetes as co-morbid condition (HR 1.06; 95 % CI 0.79, 1.43).

Table 2. Effect of treatment modality on survival; overall mortality and cardiovascular mortality rate on six patient groups.

Patient group	Overall mortality rate (Number/ 1000 person years)	Cardiovascular mortality rate (Number/ 1000 person years)
No DM	140	41
DM PRD	242	93
DM co-M	288	69

No DM denotes patients without diabetes mellitus
DM PRD denotes patients with diabetes as primary renal disease
DM co-M denotes patients with diabetes as a co-morbid condition



Number of patients at risk (n)	0	2	4	6	8
No DM	1465	792	371	114	30
DM as PRD	281	144	42	12	3
DM as co-morb	107	44	18	5	0

Figure 1: Kaplan Meier; Survival of patients with diabetes as primary renal disease (DM PRD) compared to patients with diabetes as a co-morbid condition and patients without diabetes mellitus.

The effect of treatment modality on survival

Thirty-seven percent of patients started on PD (N= 684). Five hundred and fifty five patients had no diabetes, 102 patients had diabetes as primary renal disease and

27 patients had diabetes as a co-morbid condition. After 3 months a few patients switched to hemodialysis; 15 patients without diabetes, 3 patients with diabetes as primary renal disease and none of the patients with diabetes as a co-morbid condition. The highest mortality rate was observed in patients with diabetes as primary renal disease on PD (Figure 2). Following adjustment for age and gender the HR for PD patients with diabetes mellitus as primary renal disease was 2.7 (95 % CI 2.0, 3.7) and 1.2 (95 % CI 0.7, 2.1) for PD patients with diabetes as a co-morbid condition compared to the reference group of PD patients without diabetes (Table 3).

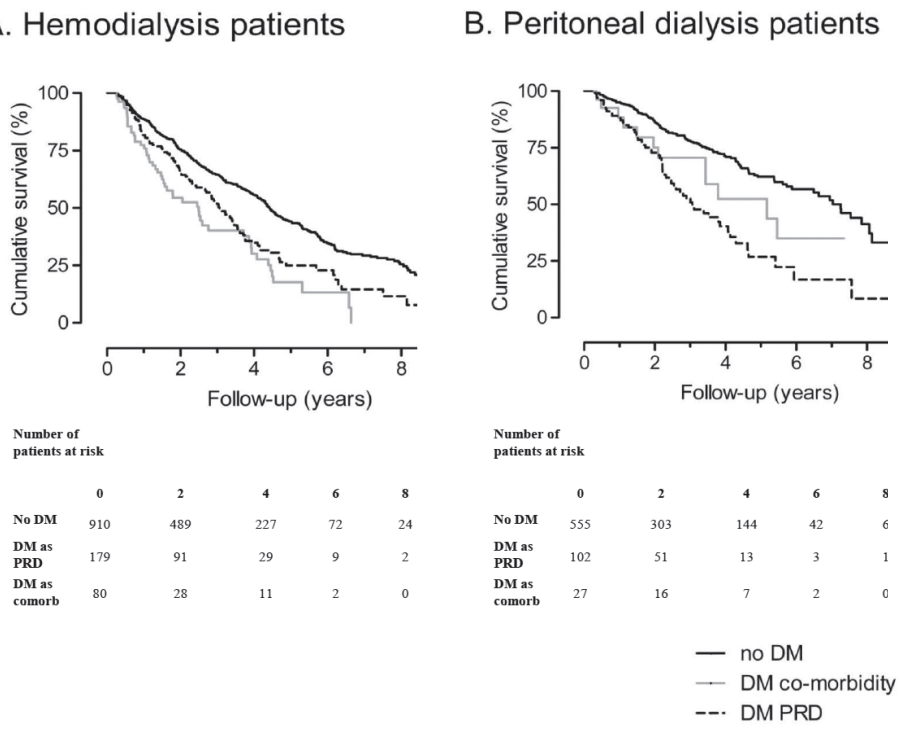


Figure 2. Kaplan Meier; Survival of patients with diabetes as primary renal disease (DM PRD) versus patients with diabetes as a co-morbid condition and patients without diabetes mellitus in patients on hemodialysis (A) and peritoneal dialysis (B).

Table 3. Effect of treatment modality on survival; a cox model on six patient groups.

Patient group	Hazard Ratio adjusted	95 % Confidence interval
Peritoneal dialysis		
No DM	1.0	
DM PRD	2.7	2.0, 3.7
DM co-M	1.2	0.7, 2.1
Hemodialysis		
No DM	1.1	0.9, 1.3
DM PRD	1.8	1.4, 2.3
DM co-M	2.0	1.4, 2.8

Data were adjusted for age and gender
No DM denotes patients without diabetes mellitus
DM PRD denotes patients with diabetes as primary renal disease
DM co-M denotes patients with diabetes as a co-morbid condition

Sixty-three percent (N=1169) of patients started on HD. Nine hundred and ten patients had no diabetes, 179 patients had diabetes as primary renal disease and 80 patients had diabetes as a co-morbid condition. After 3 months a few patients switched to peritoneal dialysis; 39 patients without diabetes, 3 patients with diabetes as primary renal disease and 5 patients with diabetes as a co-morbid condition. HD patients with diabetes as a co-morbid condition had the highest mortality rates (Figure 2). Adjusted for age and gender the HR for HD patients with diabetes as primary renal disease was 1.8 (95 % CI 1.4, 2.3) and 2.0 (95 % CI 1.4, 2.8) for HD patients with diabetes as a co-morbid condition compared to the reference group (Table 3). Further adjustment for smoking, blood pressure, body mass index, serum albumin, myocardial infarction or stroke did not materially influence the study results in HD and PD patients. After these adjustments the HR in PD patients with diabetes as primary renal disease was 2.9 (95 % CI 2.1, 4.0) and 1.2 (95 % CI 0.7, 2.3) for PD patients with diabetes as a co-morbid condition compared to the reference group. The HR in HD patients with diabetes as primary renal disease was 1.7 (95 % CI 1.3, 2.3) and 1.9 (95 % CI 1.3, 2.7) for HD patients with diabetes as a co-morbid condition compared to the reference group.

Discussion

In this cohort study we compared survival in patients with ESRD caused by diabetic nephropathy to patients with diabetes as a co-morbid condition and patients without diabetes. Survival in dialysis patients with diabetes was not different between patients with diabetes as primary renal disease and to patients with diabetes as a co-morbid condition. On HD the mortality risk in patients with diabetes as primary renal disease or diabetes as co-morbid condition was increased to a similar extent compared to PD patients without diabetes. Furthermore the mortality risk in PD patients with diabetes as primary renal disease was increased compared to patients without diabetes, whereas this was not the case in PD patients with diabetes as a co-morbid condition.

To our knowledge, this is the first study that investigated mortality in ESRD separately for patients with diabetes as a co-morbid condition and a non-diabetic primary diagnosis of renal disease of different cause. A previous study with a limited number of patients, showed that diabetic patients with a primary diagnosis of adult polycystic kidney disease exhibit a similar survival compared to patients with a primary diagnosis of diabetic nephropathy[15]. Villar et al showed that patients with diabetic nephropathy had a significant worse outcome compared to patients with glomerular nephropathy with a HR of 1.2 [8]. Other studies compared dialysis patients with diabetic nephropathy as primary renal disease to dialysis patients without diabetic nephropathy and showed impaired survival for patients with diabetic nephropathy [6,16]. Present study adds that survival in dialysis patients was not different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. These results provide important clinical information: diabetes mellitus has a very strong impact on survival even if it is not the primary cause of ESRD.

However, this finding was in contrast with our expectation since we presumed a better prognosis for patients with diabetes as a co-morbid condition compared to patients with diabetes as primary renal disease for the reason that in patients with diabetes as co-morbid condition organ damage due to diabetes mellitus might be less pronounced. In accordance with this notion, at baseline patients with diabetes as a co-morbid condition showed less retinopathy compared to patients with diabetes as a primary renal disease. However the prevalence of myocardial infarction was higher in patients with diabetes as a co-morbid condition, although this was possibly due to

different age distribution. A possible explanation for the poor outcome in patients with diabetes as a co-morbid condition could be the additional risk of diabetes in ESRD patients who were already cardiovascular compromised due to their non-diabetic renal disease. Patients with ESRD without diabetes have a high risk of cardiovascular morbidity and mortality[17], just like patients with diabetes mellitus[10,11].

We observed a difference in survival related to treatment modality of ESRD. The mortality risk in PD patients for diabetes as primary renal disease was increased compared to patients without diabetes, whereas this was not the case in PD patients with diabetes as co-morbid condition. The fact that we could not found a difference in PD patients with diabetes as a co-morbid condition could be due to limited power. In PD, dialysis fluids consist of high glucose solutions. These fluids also contained high concentration of glucose degradation products. The peritoneal absorption of glucose degradation products might enhance formation of Advanced Glycosylation End products (AGEs); a non enzymatic reaction of reducing sugars with proteins[18,19]. Accumulation of AGEs is different in PD patients compared to HD patients. A study, determining the influence of dialysis modality on plasma and tissue concentrations of a specific AGE pentosidine, showed that plasma pentosidine levels were significantly lower in PD patients compared with HD patients. In contrast, peritoneal concentrations of pentosidine were significantly higher in patients on PD compared to patients on HD[20]. AGEs may play a role in the pathogenesis of diabetic nephropathy[21]. Therefore accumulation of AGEs might be different in patients with diabetes as primary renal disease as opposed to patients with diabetes as a co-morbid condition. It might be useful to measure serum and peritoneal levels of circulating AGEs in patients with diabetes as primary renal disease compared to patients with diabetes as a co-morbid condition. Probably, PD patients with diabetes as primary renal disease may have had higher levels of (peritoneal) AGEs associated with endothelial dysfunction and atherosclerotic cardiovascular disease[22,23].

There are potential limitations in the present study. First, renal biopsies were not routinely obtained from our patients with a clinical diagnosis of diabetic nephropathy or diabetes as a co-morbid condition. Renal biopsies are the reference standard to confirm whether diabetes is indeed the primary cause of the nephropathy. However a renal biopsy is an invasive procedure with a potential risk of complications and is therefore often not performed in a routine clinical setting. The diagnosis of diabetic nephropathy was a diagnosis by exclusion and was based on the opinion

of the physician, reflecting common clinical practice. We can not exclude that some patients could have been misclassified, especially in patients with diabetes as a co-morbid condition and a primary diagnosis of renal vascular disease. In that case it can not be excluded that the diabetes has contributed largely to the renal failure. However exclusion of patients with diabetes as a co-morbid condition and a primary diagnosis of renal vascular disease did not materially influence the study results (data not shown). Second, the number of patients with diabetes either as primary renal disease or as a co-morbid condition was relatively small. Other larger and international studies had to be evaluated to confirm our study results. However, the percentage of patients with diabetes in our cohort was comparable with other studies [5]. Third, glycemic control of our patients was not documented. However treatment of NECOSAD patients was provided according to (inter)national guidelines, and it is unlikely that treatment for diabetes differed between the groups. Fourth, the number of patients who received a renal transplant was higher in patients without diabetes compared to patients with diabetes as primary renal disease or patients with diabetes as a co-morbid condition. Therefore a survival advantage might exist for patients without diabetes mellitus. Finally, some residual confounding by indication might still be present when comparing HD to PD. On peritoneal dialysis survival in patients with diabetes as a co-morbid condition was substantially better compared to patients with diabetes as primary renal disease. Despite the difficulty in categorization of patient groups these data were the best available clinical data. Furthermore, random assignment of treatment modality would hardly be feasible in patients with ESRD. Future prospective analyses are required to determine survival differences in other larger dialysis cohorts between patients with diabetes mellitus as primary renal disease and patients with diabetes as a co-morbid condition, and to establish if hemodialysis or peritoneal dialysis is the optimal treatment regimen for diabetic dialysis patients.

Further we adjusted our analyses for age and gender, while we did not for cardiovascular disease. Cardiovascular disease is most likely on the causal path between diabetes and mortality and should therefore not be adjusted for. Alternatively, it can be speculated that among patients with diabetes as co-morbid condition (if diabetes is not considered as the cause of renal disease), diabetes may also not be the main cause of cardiovascular disease as well. However, exploring this possibility and correcting the main analyses also for cardiovascular disease, did not change the results.

Conclusions

This study showed that survival in diabetic patients with ESRD was worse compared to non-diabetic patients. Mortality in patients with diabetes as primary renal disease was similar compared to patients with diabetes mellitus as a co-morbid condition. Diabetes mellitus has a very strong impact on survival even if it is not the primary cause of ESRD.

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CHAPTER 4

Survival in dialysis patients is different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition

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Abstract

Aims/hypothesis

A previous study in Dutch dialysis patients showed no survival difference between patients with diabetes as primary renal disease and those with diabetes as a co-morbid condition. As this was not in line with our hypothesis, we aimed to verify these results in a larger international cohort of dialysis patients.

Methods

For the present prospective study, we used data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry. Incident dialysis patients with data on co-morbidities (*n*=15,419) were monitored until kidney transplantation, death or end of the study period (5 years). Cox regression was performed to compare survival for patients with diabetes as primary renal disease, patients with diabetes as a co-morbid condition and non-diabetic patients.

Results

Of the study population, 3,624 patients (24%) had diabetes as primary renal disease and 1,193 (11%) had diabetes as a co-morbid condition whereas the majority had no diabetes (*n*=10,602). During follow-up, 7,584 (49%) patients died. In both groups of diabetic patients mortality was higher compared with the non-diabetic patients. Mortality was higher in patients with diabetes as primary renal disease than in patients with diabetes as a co-morbid condition, adjusted for age, sex, country and malignancy (HR 1.20, 95% CI 1.10, 1.30). An analysis stratified by dialysis modality yielded similar results.

Conclusions/interpretation

Overall mortality was significantly higher in patients with diabetes as primary renal disease as compared with those with diabetes as a co-morbid condition. This suggests that survival in diabetic patients undergoing dialysis is affected by the extent to which diabetes has induced organ damage.

Abbreviations

ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESRD	End-stage renal disease
HD	Haemodialysis
NECOSAD	Netherlands Cooperative Study on the Adequacy of Dialysis
PD	Peritoneal dialysis
RRT	Renal replacement therapy

Introduction

Diabetes mellitus has become the leading cause of end-stage renal disease (ESRD) worldwide[1–4]. In Europe 23% of the patients starting renal replacement therapy (RRT) had diabetes as the primary cause of renal disease[5]. Survival among dialysis patients with diabetes mellitus is inferior to survival of non-diabetic dialysis patients[6–8]. Due to the complications of diabetes mellitus, patients with diabetic nephropathy have the largest number of co-morbid conditions within the ESRD population when compared with non-diabetic dialysis patients[2].

We hypothesised that in patients with diabetic nephropathy, organ damage is not limited to the kidney but also might involve other organs resulting in retinopathy, neuropathy and cardiovascular complications. Since patients on dialysis with diabetes as a co-morbid condition may have less pronounced multisystem involvement, we assumed that patients with diabetes mellitus as primary renal disease might have worse survival than patients with diabetes as co-morbid condition on top of another primary renal disease. However, despite these theoretical considerations, in a previous study using data from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), we could not show that survival in dialysis patients was different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition[9]. However, that study was performed in a single country and, additionally, the sample size may have been too small to detect a survival difference. To gain power, we conducted this new study using a larger, international cohort of dialysis patients.

The primary aim of our present study was to compare the survival of dialysis patients in whom diabetes mellitus was the primary renal disease with that of dialysis patients in whom diabetes was a co-morbid condition on top of another primary renal disease. Mortality rates in these two groups were compared with mortality rates in dialysis patients who did not have diabetes mellitus. Furthermore, female patients on peritoneal dialysis (PD) with diabetes as primary renal disease have been shown to have impaired survival compared with their male counterparts[9–12]. Therefore, our second aim was to compare patient survival, stratified by sex, age and dialysis modality.

Methods

Data collection

The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry contains individual data on patients receiving RRT for ESRD. Data collection occurs annually via national and/or regional renal registries in Europe and includes data on date of birth, sex, primary renal disease, date of first RRT, history of RRT (including dates and changes of modality) and date of death. The present analysis included only data from registries that were able to provide additional data on co-morbid conditions at the start of RRT (Austria, Belgium [French-speaking part], Spain [Catalonia], Greece, Norway, Sweden and the UK)[13,14]. Approval for this study has been obtained from those individual registries. All patients of 20 years and older who started dialysis between 1998 and 2006 and who survived the first 3 months on dialysis were included. For the present analysis we chose day 91 as the start of the study because at that time most patients needed RRT as a chronic therapy and the choice of treatment modality (haemodialysis [HD] or peritoneal dialysis) can be considered to be more definitive. The following co-morbid conditions were collected and were coded as being present or absent in the medical history at initiation of dialysis: diabetes mellitus, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and malignancies. If data for all of these five types of co-morbid conditions were missing, patients were excluded from analyses. No information on medication was contained in the database.

Diabetes mellitus

For the present analysis we categorised the patients as follows: (1) non-diabetic patients, (2) patients with diabetic nephropathy as primary renal disease and (3) patients with non-diabetic origin as primary renal disease but diabetes as co-morbid condition. This distinction relied on the information provided in the database, which was based on the physician's judgment and/or a histological diagnosis.

Statistical analysis

We used descriptive statistics and performed Student's t tests and χ^2 test for direct comparisons of continuous and dichotomous outcomes. To estimate patient survival (from day 91) we performed Cox regression analyses. We restricted our survival analysis to 5 year survival because otherwise the number of patients at risk during follow-up became too small (i.e. below 10–20% of the total study population)[15]. We calculated crude all-cause mortality rates expressed as number of deaths/1,000 patient-years. Crude and adjusted HRs with 95% CIs were calculated using Cox proportional hazards models. Follow-up time was censored at recovery of renal function, kidney transplantation, loss of follow-up and at the end of the observation period (31 December 2008), whichever came first. The multivariable models used to calculate adjusted HRs included the variables age, sex, country and the presence of malignancy. Cerebrovascular and cardiovascular diseases were not included as possible confounders in our models as we considered them as potential intermediate variables between diabetes and death. However, to facilitate comparison with previous studies, we repeated our regression models with adjustment for cerebrovascular and cardiovascular disease (i.e. cerebrovascular, peripheral vascular and ischaemic heart disease). In addition, because some studies showed higher mortality for patients with type 1 diabetes compared with patients with type 2 diabetes [4, 8] we performed an additional analysis in which we differentiated the primary renal disease patients by type 1 and type 2 diabetes. The data stratified by type 1 or type 2 diabetes were not available for patients with diabetes as a co-morbid condition and therefore we performed this additional analysis only in patients with diabetes as primary renal disease. We performed a survival analysis stratified by sex and age and another analysis stratified by dialysis modality[16]. Furthermore we tested for interaction between sex, age and the presence of diabetes and tested whether or not sex or age had an additive effect on the presence of diabetes. For all analyses exposure and treatment status were used as time-independent variables. Analyses were performed using SAS 9.2 (1999–2001; SAS Institute, Cary, NC, USA).

Results

Patient characteristics A total of 15,419 patients, starting dialysis between 1998 and 2006, were included. Of these, 3,624 (24%) patients had diabetes as primary renal disease and 1,193 (11%) patients had diabetes as a co-morbid condition; the majority of patients did not have diabetes (*n*=10,602). Thirty-eight per cent of patients were women. Detailed characteristics of included patients are shown in Table 1**.** Patients with diabetes as a co-morbid condition were older at baseline (mean age 67.7 ± SD 12.6 years) compared with patients with diabetes as primary renal disease (63.0±12.8 years) and patients without diabetes (62.8±15.7 years). PD was the dialysis modality in 20% of the non-diabetic patients, in 20% of patients with diabetes as primary renal disease and in 16% of patients with diabetes as a co-morbid condition. At baseline the prevalence of cerebrovascular and cardiovascular disease did not differ between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition.

Table 1. Baseline characteristics of the study population (*n*=15,419)

Characteristic	**No DM (n=10,602)**	**DM PRD (n=3,624)**	**DM Co-M (n=1,193)**	**p value[a] (DM PRD vs DM Co-M)**
Age, continuous, mean±SD	62.8±15.7	63.0±12.8	67.7±12.6	<0.001
Age category, *n* (%)				
<70 years	6,340 (60)	2,400 (66)	580 (49)	<0.001
≥70 years	4,262 (40)	1,224 (34)	613 (51)	
Men, *n* (%)	6,615 (62)	2,156 (59)	744 (62)	0.08
HD at day 91, *n* (%)	8,521 (80)	2,909 (80)	1,007 (84)	<0.001
PRD, *n* (%)				
Diabetes		3,624 (100)		<0.001
Renal vascular disease	2,269 (21)		329 (28)	
Glomerulonephritis	2,052 (19)		189 (16)	
Other	6,278 (59)		675 (57)	
Cerebrovascular disease, *n* (%)				
No	9,335 (88)	2,860 (79)	938 (77)	0.42
Yes	1,253 (12)	760 (21)	254 (20)	

Characteristic	No DM (n=10,602)	DM PRD (n=3,624)	DM Co-M (n=1,193)	p value[a] (DM PRD vs DM Co-M)
Peripheral vascular disease, *n* (%)				
No	8,670 (82)	2,211 (61)	781 (65)	0.56
Yes	1,900 (18)	1,406 (39)	410 (34)	
Ischaemic heart disease, *n* (%)				
No	8,094 (76)	2,219 (61)	684 (57)	0.53
Yes	2,464 (23)	1,395 (38)	506 (42)	
Malignancy, *n* (%)				
No	9,329 (88)	3,372 (93)	1,036 (87)	<0.001
Yes	1,251 (12)	249 (7)	154 (13)	
Country, *n* (%)[b]				
Austria	1,962 (60)	1,098 (33)	226 (7)	<0.001
Belgium (French-speaking)	258 (68)	91 (24)	29 (8)	
Spain (Catalonia)	2,269 (72)	655 (21)	214 (7)	
Greece	1,300 (66)	494 (25)	187 (9)	
Norway	748 (78)	125 (13)	88 (9)	
Sweden	1,124 (66)	422 (25)	165 (10)	
UK	2,941 (74)	739 (19)	284 (7)	

[a]*p* values for DM as PRD vs DM as co-morbidity
[b]Percentages are row percentages
Co-M, co-morbid condition; DM, diabetes mellitus; PRD, primary renal disease

Mortality

During 5 year follow-up, 7,584 (49%) patients of the total group died. Mortality rates per patient group are shown in Table 2**.** Twenty-six per cent of patients (*n*=2,704) without diabetes received a renal transplant compared with 13% (*n*=479) of patients with diabetes as primary renal disease and 13% (*n*=152) of patients with diabetes as a co-morbid condition. Other reasons for censoring during follow-up were end of the study period (27%) and loss to follow-up (2.4%). Evaluating the loss to follow-up in more detail showed that this loss was 2.7% in patients without diabetes, 1.7% in patients with diabetes as primary renal disease and 2% in patients with diabetes as co-morbid condition.

Table 2. Overall mortality rates

Patient group	Overall mortality rate (deaths/1,000 patient-years)		
	No DM	DM PRD	DM Co-M
All	151.4	226.9	233.5
<70 years	89.9	187.3	158.0
≥70 years	250.6	316.9	317.0
Women	148.2	243.8	225.3
Men	153.5	215.9	238.6
HD	160.0	231.0	233.2
PD	118.9	210.7	235.2

Co-M, co-morbid condition; DM, diabetes mellitus; PRD, primary renal disease

Results from the survival analysis are presented in Table 3 and Fig. 1. Mortality in patients with diabetes as primary renal disease (HR 1.61, 95% CI 1.53, 1.69) or as a co-morbid condition (HR 1.34, 95% CI 1.24, 1.45) was increased compared with that in non-diabetic patients. Mortality was higher in patients with diabetes as primary renal disease than in patients with diabetes as a co-morbid condition (HR 1.20, 95% CI 1.10, 1.30). Additional adjustments for cerebrovascular and cardiovascular events did not materially change these results. An additional analysis in which we differentiated the patients with diabetes as primary renal disease by type 1 and type 2 diabetes showed a higher mortality in patients with type 1 diabetes (HR 1.45, 95% CI 1.30, 1.61). In patients with diabetes as primary renal disease, for both type 1 diabetes (HR 2.17, 95% CI 1.97, 2.39) and type 2 diabetes (HR 1.50, 95% CI 1.42, 1.59) mortality was higher compared with non-diabetic patients. Furthermore, mortality in patients with type 1 or type 2 diabetes as primary renal disease was higher compared with patients with type 1 or type 2 diabetes as a co-morbid condition, with HRs of 1.62 (95% CI 1.44, 1.82) and 1.12 (95% CI 1.03, 1.22), respectively.

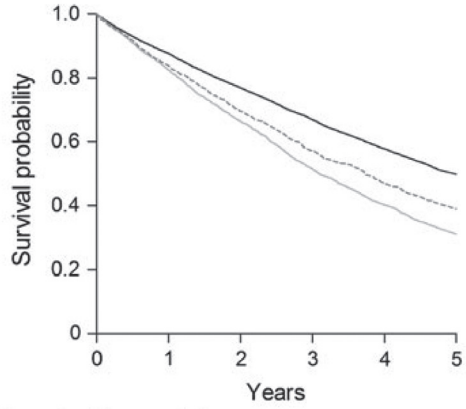
Table 3. HRs comparing mortality in dialysis patients in whom diabetes was the primary renal disease with patients in whom diabetes was a co-morbid condition

Patient group	N	Crude HR (95% CI)	Adjusted HR (95% CI)a	Adjusted HR (95% CI)b
Overall				
No DM	4,608	1 (reference)	1 (reference)	1 (reference)
DM PRD	2,236	1.51 (1.43, 1.59)	1.61 (1.53, 1.69)	1.51 (1.43, 1.59)
DM Co-M	740	1.55 (1.44, 1.68)	1.34 (1.24, 1.45)	1.26 (1.16, 1.36)
DM PRD vs DM Co-M		0.97 (0.89, 1.05)	1.20 (1.10, 1.30)	1.20 (1.11, 1.31)
Women				
No DM	1,722	1 (reference)	1 (reference)	1 (reference)
DM PRD	948	1.66 (1.53, 1.79)	1.66 (1.53, 1.80)	1.52 (1.40, 1.65)
DM Co-M	274	1.53 (1.35, 1.74)	1.32 (1.16, 1.50)	1.18 (1.04, 1.35)
DM PRD vs DM Co-M		1.09 (0.95, 1.24)	1.25 (1.09, 1.43)	1.29 (1.12, 1.48)
Men				
No DM	2,886	1 (reference)	1 (reference)	1 (reference)
DM PRD	1,288	1.42 (1.33, 1.51)	1.58 (1.48, 1.69)	1.50 (1.40, 1.61)
DM Co-M	466	1.57 (1.43, 1.73)	1.35 (1.23, 1.49)	1.30 (1.18, 1.43)
DM PRD vs DM Co-M		0.90 (0.81, 1.00)	1.17 (1.05, 1.30)	1.16 (1.04, 1.29)
Age <70 years				
No DM	1,687	1 (reference)	1 (reference)	1 (reference)
DM PRD	1,282	2.10 (1.95, 2.26)	1.96 (1.82, 2.11)	1.78 (1.64, 1.92)
DM Co-M	263	1.77 (1.55, 2.01)	1.51 (1.32, 1.72)	1.39 (1.22, 1.58)
DM PRD vs DM Co-M		1.19 (1.04, 1.36)	1.30 (1.13, 1.48)	1.28 (1.12, 1.47)
Age ≥70				
No DM	2,921	1 (reference)	1 (reference)	1 (reference)
DM PRD	954	1.28 (1.19, 1.37)	1.35 (1.25, 1.46)	1.30 (1.21, 1.41)
DM Co-M	477	1.28 (1.16, 1.41)	1.25 (1.14, 1.38)	1.19 (1.08, 1.35)
DM PRD vs DM Co-M		1.00 (0.89, 1.12)	1.08 (0.96, 1.21)	1.09 (0.98, 1.22)

[a]Model adjusted for age, sex, country and malignancy

[b]Model additionally adjusted for cerebrovascular and cardiovascular disease

Co-M, co-morbid condition; DM, diabetes mellitus; PRD, primary renal disease



Number of patients at risk						
No DM	10,580	9,371	8,048	6,884	5,484	4,918
DM PRD	3,621	3,094	2,461	1,892	1,451	1,102
DM Co-M	1,190	1,005	811	646	528	418

Figure 1. Cox regression 5 year survival stratified by the three different patient groups based on diabetic status: .no diabetes (black line); diabetes as co-morbidity (dashed line); diabetes as primary renal disease (grey line). Model adjusted for age, sex, country and malignancy. Co-M, co-morbid condition; PRD, primary renal disease

Survival analysis stratified by sex and age

In both women and men mortality was higher in patients with diabetes as primary renal disease compared with patients with diabetes as a co-morbid condition (HR 1.25, 95% CI 1.09, 1.43 and HR 1.17, 95% CI 1.05, 1.30, respectively) (Table 3). No formal interaction between sex and diabetes status was found (p=0.18).

In patients aged <70 years, mortality was higher in patients with diabetes as primary renal disease than in patients with diabetes as a co-morbid condition (HR 1.30, 95% CI 1.13, 1.48), whereas this effect was smaller in patients aged ≥70 years (HR 1.08, 95% CI 0.96, 1.21). The interaction between age and diabetes status was statistically significant (p<0.001), meaning that higher age attenuated the effect of diabetes on survival.

Survival analysis stratified by dialysis modality

Twenty per cent of patients started RRT on PD (***n***=3,097). Compared with the reference group of PD patients without diabetes, the HR for mortality was 1.95 (95% CI 1.73, 2.20) in patients with diabetes as primary renal disease on PD and 1.73 (95% CI 1.58, 1.89) in patients with diabetes as primary renal disease on HD. We stratified our analysis by sex and age and showed that mortality in women and men, younger (age <70 years) and older (age ≥70 years) patients was the highest in patients with diabetes as primary renal disease on PD (Figure. 2). When examining the specific group of older female patients (age ≥70 years) with diabetes as primary renal disease in more detail, we found an adjusted HR of 1.41 (95% CI 1.08, 1.84) for patients receiving PD vs HD. Similar results were found in older female patients (age ≥70 years) with diabetes as a co-morbid condition: HR of 1.40 (95% CI 0.87, 2.24) for patients receiving PD vs HD. However, for this group the difference did not reach statistical significance. Additional adjustment for cerebrovascular and cardiovascular disease did not materially influence the study results (data not shown).

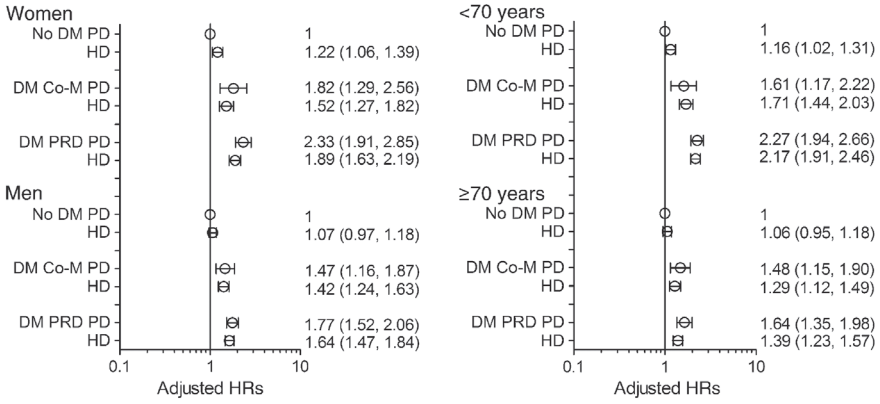


Figure 2. HRs (95% CIs) in HD and PD patients comparing mortality in dialysis patients with diabetes as primary renal disease with patients with diabetes as co-morbid condition, stratified for sex and age. Data were adjusted for age, sex, country and malignancy. Co-M, co-morbid condition; DM, diabetes mellitus; PRD, primary renal disease

Discussion

In this large European cohort study in dialysis patients we compared survival between patients with diabetes as the primary cause of renal failure to patients with diabetes as a co-morbid condition. Mortality in patients with diabetes either as primary renal disease or as a co-morbid condition was clearly higher than in non-diabetic patients. We showed that overall mortality was higher in patients with diabetes as primary renal disease as compared with those with diabetes as a co-morbid condition.

There is no doubt that diabetes contributes to mortality in dialysis patients. However, most earlier studies did not take into account the difference between patients with diabetes as primary renal disease and diabetes as a co-morbid condition[17–22]. In the NECOSAD study, a smaller study of Dutch incident dialysis patients (*n*=1,853) we did not find a difference in mortality between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. In this NECOSAD study, 15% (*n*=281) of patients had diabetes as primary renal disease, 6% had diabetes as a co-morbid condition (*n*=107) and the remaining 79% did not have diabetes (*n*=1,465). Mortality was not higher in patients with diabetes as primary renal disease compared with patients with diabetes as a co-morbid condition (HR 1.06, 95% CI 0.79, 1.43). Although the analysis in NECOSAD did not show a clear effect on mortality, the results from the present study fit in the margins of uncertainty from the NECOSAD study (i.e. CIs overlap). This means that the apparent difference in study results might reflect the low power of the NECOSAD study[9].

In the present larger cohort study we showed that mortality rates were highest in patients with diabetes as primary renal disease. Our results were in line with our initial hypothesis. In diabetic ESRD patients organ damage is not limited to the kidney but involves multisystem micro- and macrovascular complications, and these complications may be more pronounced in patients with diabetes as primary renal disease than in patients with diabetes as a co-morbid condition. This increased vascular damage may be due to longer diabetes duration in patients with diabetes as primary renal disease compared with patients with diabetes as a co-morbid condition. Unfortunately in our data set we had no information on duration of diabetes. Although no clear differences in the prevalence of vascular co-morbidities between diabetes as primary renal disease and diabetes as a co-morbid condition were shown, it should be kept in mind that patients with diabetes as primary renal

disease were almost 5 years younger. Several sensitivity analyses were performed to assess the robustness of our findings. First, a sensitivity analysis excluding patients with diabetes as a co-morbid condition and a primary diagnosis of renal vascular disease yielded similar results. Second, a sensitivity analysis excluding patients with a primary diagnosis of glomerulonephritis yielded similar results. Finally, a sensitivity analysis excluding patients with malignancy showed similar results. The difference in survival between diabetes as primary renal disease and diabetes as a co-morbid condition was a consistent finding across sex and age categories and initial treatment modality. Since this is a comparison according to disease status, this comparison cannot be randomised. Such comparisons are prone to confounding, which we tried to deal with by adjustments in a statistical model. We cannot, however, rule out that residual confounding is present. Late referral of patients with chronic kidney disease to a nephrologist is associated with increased morbidity and mortality[23–25]. It has been shown that pre-ESRD nephrologist care for more than 12 months is more frequent in patients with diabetes as a co-morbid condition than in patients with diabetes as primary renal disease (53.5% and 46.4%, respectively)[26]. It might be that differences in pre-dialysis care contributed to a worse survival for patients with diabetes as primary renal disease in our study, which emphasises the need for optimal pre-dialysis care in patients with diabetes as primary renal disease.

Previous studies showed impaired survival for older diabetic women on PD[6, 10, 11, 27, 28]. In line with these studies we also showed higher mortality in women aged ≥70 years with diabetes as primary renal disease who were treated with PD compared with their counterparts on HD. A similar, but not statistically significant, trend was found in patients with diabetes as a co-morbid condition. It could be speculated that in older diabetic female patients with vascular complications (e.g. heart failure) the preferred treatment modality is PD, with the aim of avoiding haemodynamic instability during dialysis. However, in our study, cardiovascular complications, cerebrovascular and peripheral vascular disease, but not ischaemic heart disease, at baseline were significantly more prevalent in older female diabetic HD patients compared with PD patients. Although adjustment for differences in cardiovascular disease did not change the observed difference in mortality between older female HD and PD patients, we cannot rule out the possibility that residual confounding is present.

The major strength of this study is that it is based on a large cohort of incident dialysis patients with a differentiation of the subtype of diabetes either as diabetes as primary

renal disease or as diabetes as a co-morbid condition. Furthermore, this cohort is based on well-established national and regional registries. Additionally, because it is based on patients from various countries, the probability of systematic biases due to selection or healthcare systems is reduced.

This study has potential limitations. First, the ERA-EDTA Registry does not include data such as residual renal function, ethnicity and difference between type 1 and type 2 diabetes in patients with diabetes as a co-morbid condition. We performed a sensitivity analysis in which we differentiated the patients with primary renal disease by type 1 and type 2 diabetes, showing that mortality was higher in patients with both type 1 and type 2 diabetes in whom diabetes was the primary renal disease compared with those in whom diabetes was a co-morbid condition. This suggests that differences in the underlying pattern of diabetes (type 1 or type 2) cannot fully account for the difference in mortality found between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. Moreover, the availability of type of diabetes for the whole cohort would not qualitatively have changed our results and conclusion. When comparing the patients with type 1 and type 2 diabetes as primary renal disease the highest mortality was found for patients with type 1 diabetes, in line with other studies[4, 8]. Importantly, information on glycaemic control was unavailable. The (international) guidelines for treating diabetes do not differ for patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition, so it is unlikely that glycaemic targets differed between these groups. Although glycaemic targets do not differ between these two diabetic patient groups, we cannot exclude the possibility that a difference in HbA_{1c} level might exist between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition, and this might translate into differences in mortality[29–34]. Increased vascular damage in patients with diabetes as primary renal disease might be therefore due to poorer glycaemic control compared with patients with diabetes as a co-morbid condition.

Second, routine renal biopsies were probably not performed in all patients with a clinical diagnosis of diabetes and ESRD. Although a histological diagnosis would add to the robustness of the study results, a renal biopsy is an invasive procedure with the risk of serious complications[35]. Biopsies are not routinely performed in clinical practice and the distinction between diabetes as primary renal disease and diabetes as a co-morbid condition will often be based on the opinion of the physician as is

common in clinical practice. In a study comparing the clinical vs histological diagnosis of diabetic nephropathy in 84 Austrian patients with type 2 diabetes, a high sensitivity and specificity for the clinical diagnosis of diabetic nephropathy was shown[36].

In conclusion, we showed that mortality in dialysis patients with diabetes either as primary renal disease or as a co-morbid condition is higher compared with non-diabetic dialysis patients, with the highest mortality in patients with diabetes as primary renal disease. Therefore, in studies comparing diabetic patients (as a total group) with non-diabetic patients, survival of the patients with diabetes as primary renal disease may be overestimated. The difference in survival between patients with diabetes as primary renal disease and diabetes as a co-morbid condition was a consistent finding across sex and age categories and initial treatment modality. This suggests that survival in diabetes patients with ESRD is affected by the extent to which the diabetes has induced organ damage. Future studies should elucidate the causal mechanisms underlying this difference in survival as this will have relevance to intervention and management of this increasing patient population.

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CHAPTER 5

Predicting mortality in patients with diabetes starting dialysis

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Abstract

Background

While some prediction models have been developed for diabetic populations, prediction rules for mortality in diabetic dialysis patients are still lacking. Therefore, the objective of this study was to identify predictors for 1-year mortality in diabetic dialysis patients and use these results to develop a prediction model.

Methods

Data were used from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter, prospective cohort study in which incident patients with end stage renal disease (ESRD) were monitored until transplantation or death. For the present analysis, patients with DM at baseline were included. A prediction algorithm for 1-year all-cause mortality was developed through multivariate logistic regression. Candidate predictors were selected based on literature and clinical expertise. The final model was constructed through backward selection. The model's predictive performance, measured by calibration and discrimination, was assessed and internally validated through bootstrapping.

Results

A total of 394 patients were available for statistical analysis; 82 (21%) patients died within one year after baseline (3 months after starting dialysis therapy). The final prediction model contained seven predictors; age, smoking, history of macrovascular complications, duration of diabetes mellitus, Karnofsky scale, serum albumin and hemoglobin level. Predictive performance was good, as shown by the c-statistic of 0.810. Internal validation showed a slightly lower, but still adequate performance. Sensitivity analyses showed stability of results.

Conclusions

A prediction model containing seven predictors has been identified in order to predict 1-year mortality for diabetic incident dialysis patients. Predictive performance of the model was good. Before implementing the model in clinical practice, for example for counseling patients regarding their prognosis, external validation is necessary.

Introduction

Diabetic patients have a high risk of developing micro- and macrovascular complications such as retinopathy, (cardio)vascular disease and renal disease. According to data in the ERA-EDTA Registry, 23 % of the incident end-stage renal disease (ESRD) patients had diabetes as primary renal disease[1]. Survival of diabetic dialysis patients appears inferior compared to ESRD patients without diabetes[2,3], mainly due to cardiovascular disease[4]. Mortality in the diabetic dialysis population is high but varies significantly among patients[5,6].

A prediction model for mortality in diabetic dialysis patients could be a helpful tool in clinical decision-making. For example, it could inform patients about their mortality risk and guide doctors and patients in their decisions on treatment. Furthermore, a prediction model that could accurately stratify patients according to their mortality risk would be useful to evaluate the composition of patients treated in a given center and provide the opportunity to compare baseline risks in comparative studies[7]. Finally, it could aid in designing a clinical trial and selecting subjects for inclusion[8]. Although some prediction models have been developed in patients with diabetes and diabetic nephropathy to predict ESRD[9–13], no prediction model exists in diabetic dialysis patients to predict mortality.

The primary aim of this study was to construct a prediction model to predict 1-year mortality in diabetic dialysis patients. We aimed to include easily obtainable patient characteristics, co-morbid conditions and basic laboratory variables, for the model to be convenient for clinical practice.

Materials and Methods

Study population

Data were collected from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter, prospective cohort study in which 38 dialysis centers throughout the Netherlands participated. Incident adult patients were included at the start of dialysis treatment, between 1997 and 2007. Follow-up data on death were available until 2011. In the present analysis, all patients with diabetes mellitus (patients with diabetic nephropathy and patients with non- diabetic origin of

ESRD but diabetes as co-morbid condition) at 3 months after the start of dialysis, which was considered the baseline of the study, were included. We chose 3 months as the start of the study for several reasons: First, at 3 months renal replacement therapy is likely to be a chronic therapy and the choice of treatment modality, hemodialysis or peritoneal dialysis, would be more definitive[14]. Furthermore, patients who recovered or died from acute renal failure within 3 months were excluded from the analysis in this way, creating a more robust model. Finally, at 3 months the clinical condition of patients is more likely to have stabilized and prognostic questions may arise at this point in time. Patients were monitored until renal transplantation or death. Informed consent was obtained before inclusion, and the Medical Ethics Committees of all participating centers approved the study (Maasstad Hospital Rotterdam, Deventer Hospital Deventer, Sint Lucas Andreas Hospital Amsterdam, Academic Medical Center Amsterdam, Maxima Medical Center Veldhoven, Catharina Hospital Eindhoven, Medical Center Haaglanden Den Haag, University Medical Center Groningen, Kennemer Gasthuis Haarlem, Atrium Medical Center Heerlen, Medical Center Leeuwarden, Leiden University Medical Center Leiden, Elisabeth Hospital Tilburg, University Medical Center Utrecht, Antonius Ziekenhuis Nieuwegein, Hospital Gelderse Vallei Ede, Haga Hospital Leyenburg Den Haag, Academic Hospital Maastricht, Jeroen Bosch Hospital Den Bosch, Medisch Spectrum Twente Enschede, Albert Schweitzer Hospital Dordrecht, Alysis Zorggroep Rijnstate Hospital Arnhem, Dianet Dialysis Center Lunetten Utrecht, Canisius Wilhelmina Hospital Nijmegen, Vie Curi Medical Center Venlo, Leveste Scheper Hospital Emmen, Dianet Dialysis Center Holendrecht Amsterdam, Haga Hospital Rode Kruis Den Haag, Rijnland Hospital Leiderdorp, Admiraal de Ruyter ziekenhuis Goes, Medical Center Alkmaar, Laurentius Ziekenhuis Roermond, Dialysis Center 't Gooi Hilversum, Groene Hart Hospital Gouda, Westfries Gasthuis Hoorn, TergooiHospitals Hilversum, Martini Ziekenhuis Groningen, Zaans Medical Center Zaandam).

Outcome and candidate predictors

The outcome of interest was all-cause mortality within one year after inclusion (3 months). To minimize the risk of overfitting which would harm generalizability of the model and lead to poor performance in new datasets, the number of candidate predictors considered in the analysis should be limited[15,16] . Also, decisions regarding the list of candidate predictors should be made independently of the data

at hand[17]. Therefore, we composed a limited candidate predictor list a priori, that is prior to the statistical modelling process. To this end, we first made a selection of promising prognostic factors for one year mortality among incident dialysis patients with diabetes mellitus from the available variables based on a literature review. Next, we reduced this list by combining the rankings of these prognostic factors by both nephrologists and endocrinologists, resulting in the candidate predictors as described below.

Age, sex, smoking status and data on comorbidity were collected at the start of dialysis therapy. Currently smoking or smoking cessation in the three months preceding dialysis initiation was considered smoking. Comorbidity data included a history of cerebral vascular accident, myocardial infarction and peripheral vascular disease with or without amputation. At three months, laboratory values and other clinical parameters were collected. For each patient, data on diabetes mellitus were collected. To indicate the severity of diabetes mellitus, insulin-dependency, a history of diabetic retinopathy for which laser therapy was performed and patient-reported duration of diabetes mellitus were considered for the analysis. Body mass index, blood pressure and levels of hemoglobin, phosphate and serum albumin were included in the analysis. In addition, residual renal function was expressed as the residual glomerular filtration rate (rGFR), which was calculated as the mean of 24-hour creatinine and urea clearance corrected for body surface area (ml/min/1.73 m2). Finally, dialysis treatment modality (HD / PD) and the Karnofsky scale, which is a clinician-assessed scale of functional status, were included. The Karnofsky scale consists of ten levels, ranging from 10 (moribund) to 100 (normal, without limitations).

Next, the list of candidate predictors was further reduced as follows. Instead of including all selected comorbidities separately, history of cerebral vascular accident (CVA), myocardial infarction (MI) and peripheral vascular disease with amputation were combined into one predictor to indicate whether a patient had suffered from macrovascular complications. Systolic blood pressure was chosen to represent blood pressure, as this has been shown to be most predictive of mortality in dialysis patients[18]. Next, although the Karnofsky scale was registered as a categorical variable, it is of an ordinal nature and it was therefore included as a continuous variable [17]. Finally, although data on measured residual GFR (rGFR) based on 24-hour urine collection were available in NECOSAD, rGFR was not included in the main analysis since rGFR is not measured everywhere in this way as a standard procedure.

Including rGFR in a prediction rule would therefore make it less practical for use in clinical practice and generalizability would be questionable. Indeed, also in the NECOSAD database a large part (18.8%) of this variable was missing. This would mean no prediction could be made for one out of every five patients. However, as most researchers and clinicians would agree rGFR could potentially be an important predictor for mortality in kidney patients and should not be overlooked a priori, we did perform an additional analysis where rGFR was included in the candidate variable list (see below). In total, these procedures resulted in a list of 14 candidate predictors for the main analysis.

Statistical analyses

Baseline characteristics were summarized as means with standard deviations for continuous variables and as numbers with valid percentages for categorical variables, unless stated otherwise. Missing data were handled by multiple imputation methods using the fully conditional specification[19–21]. All predictors were imputed through linear or logistic regression as appropriate, with two exceptions: the square root of duration of DM was imputed because of non-normality, and the Karnofsky scale was imputed continuously. All candidate predictor variables were entered in a multivariate logistic regression analysis, with one-year mortality as dependent variable. Backward selection with the Akaike Information Criterion (AIC) stopping rule[17,22] was used to identify the most significant independent predictors. In logistic regression analysis, the AIC stopping rule corresponds to a p-value <0.157 for predictor variables with one degree of freedom. Subsequently, forward selection was applied to check stability of the results. Results were pooled over imputed datasets according to Rubin's rules[23,24].

The model's predictive performance was assessed by estimating calibration and discrimination of the model. Calibration indicates how well the model's predictions agree with the observed outcomes and was represented by the calibration slope (which is the regression coefficient of the logistic regression model with the prognostic index as the only predictor)[17,25]. Discrimination indicates how well the model can distinguish between individuals with and without the outcome and was represented by Harrell's c-statistic (which is equal to the area under the receiver operator curve (AUC) for logistic regression analysis)[15,17]. The apparent predictive performance, meaning the performance in the data that were used to develop the model, generally

overestimates the predictive performance in new patients. Therefore, validation of the model's predictive performance is necessary to control for this potential overfitting, and internal validation was established through bootstrapping[26,27]. The bootstrapped calibration slope was used as a shrinkage factor to adjust the model for potential overfitting and adjusted coefficients were computed[17].

To assess the robustness of the model a number of sensitivity analyses were performed by (1) checking for non-linearity of continuous variables, (2) excluding all patients with competing endpoints that were treated as alive in the original analysis, (3) including rGFR in the candidate list after imputation of missing values, (4) extending the outcome to 3-year mortality and (5) relaxing the backward selection removal criterion. Bootstrap analysis was performed using the Design package in R[28,29] All other statistical analyses were performed using SPSS (version 20.0; SPSS Inc, Chicago, IL).

Results

Baseline characteristics

Baseline characteristics of the study population of diabetic incident dialysis patients (n=394 out of a total of 2051 incident dialysis patients in NECOSAD) are shown in Table 1. Patients had a median age of 65 years (interquartile range 54-72) and were on average overweight (mean BMI 26.6 (5.0)). In 69% of patients the initial treatment modality was hemodialysis. Thirty-two percent of patients had macrovascular complications and 47% of patients had clinically relevant microvascular complications (retinopathy for which laser coagulation was performed). Eighty-two patients (21%) died within one year after inclusion.

Table 1. Baseline characteristics of the study population

Baseline characteristics (n=394)	
Sex (% male)	55
Age at start dialysis (median, years)	65.3 (54.4-72.4)
BMI (kg/m²)	26.6 (5.0)
Smoking status (current or recently quit) (%)	21
BP (mmHg)	
Systolic	149 (21)
Diastolic	78 (10)
Comorbidities (%)	
Cerebrovascular accident	13
Myocardial infarction	18
Peripheral vascular disease with amputation	5
Macrovascular complications	32
Severity of DM	
Insulin-dependency (%)	64
Duration of DM (median, years)	14 (7-22)
Retinopathy (lasercoagulation) (%)	47
Treatment modality (% HD)	69
Karnofsky scale (%)	
0-40	4
50-70	47
80-100	49
Laboratory values	
Hemoglobin (g/dl)	11.1 (1.6)
Phosphate (mmol/l)	1.8 (0.5)
Serum albumin (g/l)	34.9 (5.0)
rGFR (ml/min per 1.73 m²)	4.1 (2.9)

Age and duration of DM are presented as median (interquartile range). Other continuous predictors are presented as means (SD); categorical variables are presented as %.

Abbreviations: BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HD, hemodialysis; rGFR, residual glomerular filtration rate.

Predictive variables for 1-year mortality

Fourteen candidate predictors (age, sex, BMI, smoking status, systolic blood pressure, macrovascular complications, insulin dependency, duration of diabetes, retinopathy, treatment modality, Karnofsky scale, hemoglobin level, serum phosphate and serum albumin) were included in this analysis. Percentage of missing data was on average 1.9% with a maximum of 8.9% for duration of diabetes mellitus. Five imputed datasets were created. Backward selection with the Akaike information criterion (AIC) stopping rule resulted in the final model with seven predictors; age, smoking status, Karnofsky scale, history of macrovascular complications, duration of DM, serum albumin and hemoglobin level. The pooled estimation results are presented in Table 2. Forward selection led to the same results, indicating stability of results.

Table 2. Predictive variables for 1-year mortality based on multivariate regression analysis

Predictor	**B**	**S.E.**	**P-value**	**B_adj**
Age (years)	0.047	0.014	0.001	0.042
Smoking	0.631	0.364	0.083	0.570
Macrovascular complications	1.195	0.291	<0.001	1.078
Duration of DM (years)	0.026	0.013	0.047	0.023
Karnofsky scale	-0.043	0.010	<0.001	-0.039
Hemoglobin level (g/dl)	-0.186	0.097	0.056	-0.168
Albumin level (g/l)	-0.060	0.029	0.042	-0.054

Abbreviations: B, estimated coefficient; S.E., standard error of estimate; B_adj, estimated coefficient adjusted for overfitting.

All predictor variables in the final model had estimated coefficients in the expected directions. For example, smoking status had a positive coefficient, so a smoking patient has a higher probability of dying within a year. On the other hand, Karnofsky scale had a negative coefficient, so the higher the Karnofsky scale of a patient, the lower the probability of dying within a year.

To illustrate the predictions of the model, consider a non-smoking diabetic dialysis patient of 60 years old, with a previous history of myocardial infarction and a duration of diabetes mellitus of 14 years. His Karnofsky scale was 70, his Hb level was 10.5 g/dl and his albumin level was 35 g/l. This resulted in a 1-year mortality risk of 27% (95%-CI: 18%-37%). The same patient, but 10 years older and with a Karnofsky

scale of only 40, would have a 1-year mortality risk of 68% (95%-CI: 51%-81%). See Supplementary appendix 1 with Supplementary Table A.1 for computational details and Supplementary appendix 2 for a risk calculator.

Validation of the model

To illustrate the calibration of the model, the model was used to predict the risk of one-year mortality for every patient in each imputed dataset used to develop the model and pooled over imputations. Then predicted mortality risk was divided into quartiles from very low to high risk, where the very low risk category represented an average risk of less than 5%, while the average predicted risk in the high risk category was about 50%. Calibration of the model was investigated by comparing observed to predicted risk across the four risk strata and is shown in Figure 1.

Discrimination was assessed by calculating the c-statistic using the receiver operator curve (ROC) for each imputed dataset and pooling results. Figure 2 shows the ROC of the logistic regression model. The c-statistic of the model was 0.810 [0.759-0.860], indicating good discriminative ability. That is, in 81% of the cases the model will assign the highest mortality risk to a patient that dies within a year compared to a random patient that is still alive after a year.

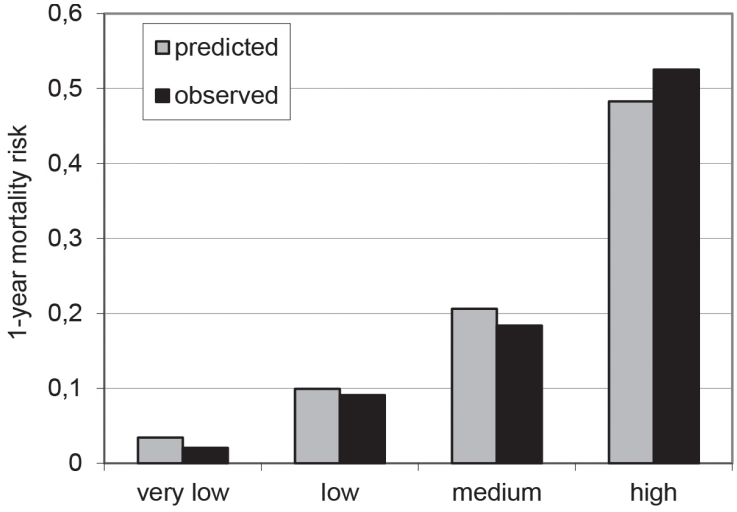

Figure 1. One-year mortality according to risk quartiles. Grey bars represent predicted 1-year mortality risk and black bars represent observed 1-year mortality risk.

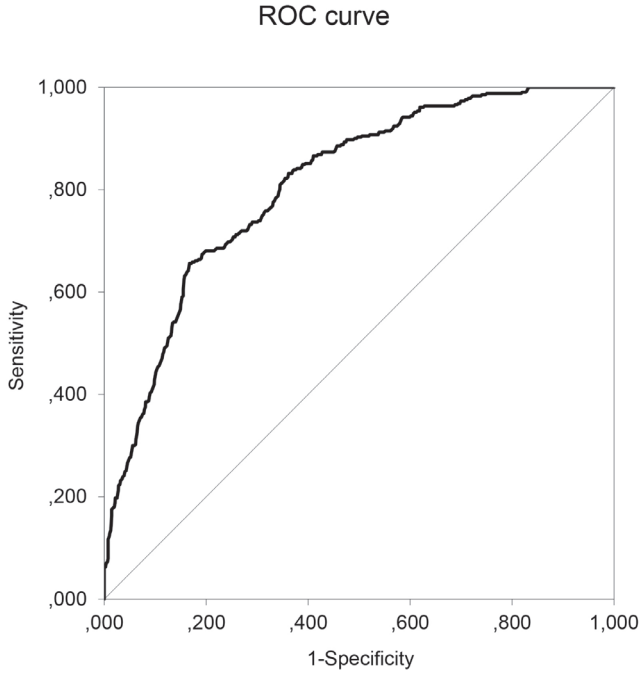

Figure 2. Receiver operating characteristic curve for the logistic regression model. The c-statistic was 0.810.

Our model was subsequently internally validated by bootstrapping in each imputed dataset after which results were pooled. Table 3 compares the apparent performance of the full model (before backward selection), the apparent performance of the final model, and the bootstrapped performance of the final model. The bootstrapped performance is an indication of the external performance, so how the model will perform in a new set of patients.

Table 3. Internal validation: apparent & optimism-corrected performance

Performance measure	full model	final model	bootstrap
Calibration: slope	1.000	1.000	0.903
Discrimination: c-statistic	0.816	0.810	0.790

The c-statistic of the final model was 0.810, which is only slightly lower than that of the full model (0.816). Hence, the final seven predictors were able to discriminate almost as well as the total set of fourteen predictors, justifying the backward selection procedure. By definition, the calibration slope equalled 1 in the original data. After bootstrapping the calibration slope was 0.903, indicating that some overfitting was present. However, it did not substantially affect discrimination, as the c-statistic was still 0.790. For clinical purposes, the bootstrapped calibration slope estimate can be used as a shrinkage factor to compute more reliable parameter estimates, which are presented in the final column of Table 2.

Next, several sensitivity analyses were performed to check stability of results. First, to test for non-linearities, quadratic terms of the continuous predictors in the final model were added one by one. None of them were found significant and discrimination did not improve substantially, with a maximum c-statistic of 0.812. Second, patients with competing endpoints such as transplantation or refusal to participate within one year were treated as alive, although their actual status at one year was unknown. Excluding these patients (n=33) from the analysis did not alter results; the same seven predictors constituted the final model with similar coefficients and model performance. Third, residual GFR was added to the candidate predictor list. In 18.8% of the cases rGFR was missing. Because of non-normality, rGFR was imputed as a square root. It was not significant on top of the seven original predictors in the final model (point estimate of -0.068 with p=0.275), nor did it substantially improve discrimination (improvement of 0.005 in c-statistic). In an additional analysis with only patients with available rGFR,

adding rGFR did not substantially improve predictive performance of the model either (improvement of 0.007 in c-statistic). As a more concise model would be preferred in clinical practice and a recent rGFR may not be available for all patients, rGFR was hence not included in the final model. Fourth, the prediction procedure was repeated for 3-year mortality. Of the 394 patients, 174 (44%) died within three years. Backward selection resulted in predominantly the same final predictor list, where smoking status and hemoglobin level in the model were replaced by sex and therapy modality. Thus, even with a broader timeframe for the outcome, the model is quite stable. The predictive performance was slightly lower, as indicated by a c-statistic of 0.784. Finally, the backwards selection removal criterion was relaxed to p-value=0.25, which did not change the final model. Further backwards selection removal criterion to p-value=0.50, resulted in three extra predictors in the final model (sex, BMI and insulin-dependence), but only slightly improved discrimination (c-statistic=0.815). Since a smaller model is more convenient in practice, the final model with seven predictors was retained.

Discussion

In this cohort study we aimed to identify predictors for 1-year all-cause mortality in diabetic patients on dialysis treatment and used the results to develop a prediction model for this population. Three hundred and ninety four incident diabetic patients were included in this analysis and 82 patients (21%) died within one year after inclusion. Candidate predictors were selected a priori based on existing literature and clinical expertise. The final prediction model contained seven predictors; age, smoking, history of macrovascular complications, duration of diabetes mellitus, Karnofsky scale, serum albumin and hemoglobin level.

Several prediction models have been developed to predict mortality in dialysis patients. Wagner et al. developed a prediction model for 3-year mortality in incident dialysis patients and found that basic patient characteristics, co-morbid conditions and laboratory values can predict 3-year mortality with a c-statistic of 0.75[13]. Mortality in this study was somewhat lower (30%) than our 3-year mortality (44%). Holme et al. made a prediction model for total 3-year mortality in patients on hemodialysis with a c-statistic of 0.73[30]. Mortality in this study (47%) was in line with our 3-year mortality. These prediction models included diabetes mellitus as a comorbid condition.

The current prediction model adds to existing models because it is a special model for diabetic incident dialysis patients, which includes specific diabetes-related patient characteristics and co-morbid conditions. Therefore, it is probably more accurate than existing prediction models[13,30] in predicting mortality in this diabetic patient group, as indicated by the c-statistic of 0.810. This model will provide the opportunity to individualize treatment options. Furthermore it allows identifying and informing patients with the highest risk of death within one year. Also, as (novel) biomarkers for outcomes in this patient population are currently being developed[31,32], an adequate basic prediction model is a requisite for assessing the additional predictive value of these biomarkers. Note that our model is not developed as a decision-tool in a pre-dialysis setting, as for such a tool, one would need both different data and different methods. Instead, our model was developed for risk stratification, i.e., to make risk predictions for new chronic dialysis patients after the clinical situation has stabilized.

There are some potential limitations in the present study. First, although the percentage of patients with diabetes in our cohort was similar to that in other European studies[5], the number of diabetic patients was relatively small for developing a prediction model. However, we controlled for potential overfitting by limiting the number of candidate predictors and bootstrapping performance measures. Second, other risk factors - such as if dialysis was started as an elective or urgent treatment, if access for dialysis was already available and social and educational variables - have been found or hypothesized to be related to mortality in diabetic or dialysis patients but have not been included in our analysis because of data restrictions. Specific examples of promising predictors lacking in the NECOSAD data are neuropathy, HbA1c level and diabetes type. Regarding neuropathy, however, adding severity of co-morbid conditions did not seem to increase their predictive power for survival in a study comparing several commonly used co-morbidity indices[33]. As for glycaemic control, we cannot exclude that difference in HbA1c level might translate into different mortality risk[34] and could improve the predictive performance of our model. Regarding diabetes type, as information on this predictor was lacking we included insulin use in our candidate predictor list, which may have been a weaker predictor. However, even without these variables, our prediction model performs well. In contrast to an etiologic study, the value of a prediction model is not judged on individual variables, but on the quality and validity of the predictions that can be made with the variables available. Predicting outcomes is different from explaining their cause[35]. All

variables potentially associated with the outcome, not necessarily causally, can be considered in a prognostic study and confounding does not play a role[36,37]. Thus, the lack of potentially important covariates in a prognostic study means there may be room for improvement of the predictive performance, but does not invalidate the current results. Because of data restrictions we could not take all mentioned risk factors into account, but it would be an interesting future research avenue to investigate whether these also contribute prognostically, and improve the predictive performance of the current model. As a third limitation, some may argue that it might be warranted to develop separate prediction models for hemodialysis and peritoneal dialysis patients. Indeed, this may result in even better predictive performance, as it could be that predictor effects differ for PD and HD patients. However, our sample size does not suffice for developing separate models or including interaction terms with therapy modality and we therefore leave this exercise to future research. And fourth, this prediction model has not been evaluated in an external data set yet, which is a necessary condition before introducing the model in clinical practice, by means of an easy to use clinical application.

Despite these limitations this prediction model is the first model that predicts mortality in diabetic incident dialysis patients with good discriminative ability, indicated by the c-statistic of 0.810. To minimize the risk of overfitting we considered a ratio of five endpoints to one candidate predictor acceptable. As larger ratios have been suggested, we additionally controlled for overfitting with internal validation through bootstrapping. Also several sensitivity analyses were performed to check robustness of the model, which showed stability of the results. For example, even a broader time frame of the predicted outcome resulted in predominantly the same final predictor list. Furthermore, the simplicity of the model with parameters that are easily to obtain makes this prediction model potentially useful for clinical practice, for example for counseling patients regarding their prognosis, and guiding doctors and patients in their decisions on future treatment.

In conclusion; a prediction algorithm for 1-year all-cause mortality has been developed for incident diabetic dialysis patients. The performance of this model is good as indicated by good outcomes for discrimination and calibration. For future research our study results need to be evaluated in an external data set. Preferentially this prediction model would be evaluated in other international and larger cohort studies before implementing in clinical practice.

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Appendix S1. Computing individual 1-year mortality risk

To clarify how the predicted 1-year mortality risk for a certain patient can be computed from the coefficients, consider the example of a non-smoking diabetic dialysis patient of 60 years old, with a previous history of myocardial infarction and a duration of diabetes mellitus of 14 years. His Karnofsky scale was 70, his Hb level was 10.5 g/dl and his albumin level was 35 g/l. To compute his 1-year mortality risk, his prognostic index (PI) has to be computed first. This is achieved by multiplying the estimated coefficients with the values of the predictor variables of the patient and taking the sum of these multiplications, added by the intercept of the model, see Table A.1. Now, adding all B*X terms and the intercept results in a prognostic index of -0.992. Computation of a prognostic index with the current model can also be expressed as a general formula:

PI = 1.692 + 0.047*Age (+0.631 if smoking) (+ 1.195 if macrovascular complications) + 0.026*Duration of DM - 0.043*Karnofsky scale - 0.186*Hemoglobin - 0.060*Albumin

Filling out the example values of the predictor variables results in the same value for the PI:

PI = 1.692 + 0.047*60 + 1.195 + 0.026*14 - 0.043*70 - 0.186*10.5 - 0.060*35 = 1.692 - 2.684 = -0.992.

Since the prediction model is a logistic model the predicted 1-year mortality probability can then be computed by:

1-year mortality risk = exp(PI) / (1+exp(PI)).

Thus, in this example, the 1-year mortality risk is exp(-0.992)/(1+exp(-0.992))=0.37/1.37=27%. When applying the coefficients that are adjusted for overfitting (see Table 2), the predicted 1-year mortality risk of this patient would be 26%.

Table A.1. Computation of prognostic index

Predictor X	B	Value of X	B*X
Age (years)	0.047	60	2.820
Smoking	0.631	0	0.000
Macrovascular complications	1.195	1	1.195
Duration of DM (years)	0.026	14	0.364
Karnofsky scale	-0.043	70	-3.010
Hemoglobin level (g/dl)	-0.186	10.5	-1.953
Albumin level (g/l)	-0.060	35	-2.100

Abbreviations: B, estimated coefficient; X, predictor variable.

The intercept of the model was 1.692.

Appendix S.2. Risk calculator for individual 1-year mortality risk

This excel sheet calculates the predicted risk of 1-year mortality in incident diabetic dialysis patients

Please fill out:	
Age (years)	60
Smoking (0 if no, 1 if yes)	0
Macrovascular complications (0 if no, 1 if yes)	1
Duration of DM (years)	14
Karnofsky scale	70
Hemoglobin level (g/dl)	10.5
Albumin level (g/l)	35.0
Predicted risk of death within one year	**27%**
Predicted risk corrected for overfitting	**26%**

CHAPTER 6

Mortality after amputation in dialysis patients is high but not modified by diabetes status

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Abstract

Background

Survival among dialysis patients with diabetes mellitus is inferior to survival of non-diabetic dialysis patients, probably due to higher prevalence of diabetes related co-morbid conditions. One could hypothesize that these co-morbid conditions also contribute to a decreased survival after amputation in diabetic patients compared to non-diabetic patients on dialysis.

Methods

Data were collected from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter, prospective cohort study in which new patients with end stage renal disease (ESRD) were monitored until transplantation or death. Amputation rates (incident cases) were calculated in patients with and without diabetes mellitus. The primary endpoint was all cause survival after a first amputation during dialysis therapy in diabetic patients compared to non-diabetic dialysis patients with an amputation. This was formally assessed using interaction analysis (Poisson regression).

Results

During follow-up (mean duration 2.9 years), 50 of 413 diabetic patients had a new amputation (12.1 %), compared to 20 of 1553 non-diabetic patients (1.2 %). Amputation rates/ 1000 person years were 47.9 (95% CI 36.3-63.2) and 4.1 (95% CI 2.7-6.4) respectively for diabetic patients and non-diabetic patients. Amputation increased mortality risk more than fourfold, in patients without diabetes (HR 4.6, 95 % CI 2.8-7.6) as well as in patients with diabetes (HR 4.6 95% CI 3.3-6.4). No formal interaction between diabetes and amputation was found (p=0.12).

Conclusions

Amputation in dialysis patients is associated with a with a fourfold increased mortality risk; this mortality risk was similar for diabetes and non-diabetes patients. Importantly, the risk for amputation is tenfold higher in diabetes mellitus compared to non-diabetic dialysis patients.

Introduction

Diabetes mellitus is the most common underlying cause of non-traumatic amputation. The main factors associated with diabetes-related amputation are sensory neuropathy, infection and ischemia[1-5]. Another common cause of amputation is chronic kidney disease with the highest risk in patients with End Stage Renal Disease (ESRD)[6]. Furthermore, several studies have an ~10-fold increased amputation risk in diabetic dialysis patients compared to non-diabetic dialysis patients, although risk estimates show a variation among different countries[7, 8].

Studies on survival after amputation in diabetic and non-diabetic patients with and without End Stage Renal Disease (ESRD) thus far showed contrasting results. In some studies diabetes was associated with an excess mortality after amputation[9, 10], while other studies showed similar or reduced mortality in diabetic patients compared to non–diabetic patients[7, 11-15]. Another study reported a time-dependent impact of diabetes on mortality with a lower mortality in the first 2-3 years, thereafter diabetic patients had a higher mortality compared to non-diabetic patients[16]. These contrasting results might be due to different study populations, different follow-up time and different statistical approaches.

The primary aim of the present study was to compare survival after amputation in diabetic dialysis patients to non-diabetic dialysis patients, using a cohort study with long term follow-up. The secondary aim of this study was to determine the incidence of a recurrent amputation in diabetic dialysis patients.

Materials and methods

Design

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective, multicenter cohort study in 38 dialysis centres throughout the Netherlands in which incident patients with ESRD were included at the time of initiation of dialysis treatment, from January 1, 1997 until January 1, 2007. Study visits took place at the start of dialysis, at 3 months, 6 months and subsequently at 6-month intervals until the date of censoring (death, kidney transplantation or transfer to a non-participating dialysis centre) or the end of the follow-up at 1 January

2007. Data on demographic characteristics and co-morbidities were collected at the time of entry into the study. Dialysis characteristics were collected 3 months after the start of RRT and at 6 month intervals thereafter. At the 3 month visit patients were classified according to the treatment modality, i.e. hemodialysis (HD) or peritoneal dialysis (PD). The cause and type of renal disease were defined according to the criteria of the European Renal Association-European Dialysis and Transplantation Association[17]. For each patient, data on diabetes mellitus were collected such as insulin-dependency, patient-reported duration of diabetes mellitus and history of diabetic retinopathy for which laser therapy was performed. During each study visit, patients were asked if they had been operated and/or admitted to the hospital. Surgical (operation) procedures and date were documented. Furthermore hospital admissions and reason for admission were registered.

Patient selection

Patients aged ≥18 years who started with dialysis as initial renal replacement therapy were eligible for this study. Start of dialysis was considered as baseline and start of follow-up, except for analyses concerning treatment modality in which case three months was considered as baseline; the reason is that after 3 months, most patients are considered to be on a 'definitive' dialysis mode. Informed consent was obtained before inclusion. This study was approved by the Medical Ethics Committees of all participating centres.

Exposures and study outcomes

For all patients we extracted data on amputations; levels of amputations were categorized as toe(s), feet, below knee and above knee. Toe(s) and feet amputations were classified as minor amputation while below knee and above knee were classified as major amputations. Second, amputations were classified as either prevalent (present at start follow-up) or incident (during follow-up; ipsilateral amputation, contralateral amputation or both). We compared amputation rates between patients with and without diabetes mellitus. To study the effect of amputation on mortality and the also potential of effect modification by diabetes, we compared mortality rates in four groups: 1. patients without amputation and without diabetes mellitus (DM) (reference), 2. patients without amputation but with diabetes, 3. patients with amputation, without diabetes, 4.patients with both an amputation and diabetes.

Statistical analysis

Baseline variables were compared between diabetes and non-diabetes dialysis patients and expressed as proportion or mean with standard deviation. For time-to-event analysis patients were censored at time of the event under study (amputation or death), renal transplant, or end of follow-up (1 January 2007). Amputation rate was calculated as incidence rate and expressed as number of amputations/ 100 person years.

Mortality rates were compared with Poisson regression, and incidence rate ratios were estimated including 95% confidence intervals. To estimate the effect of amputation on mortality, amputation was considered a time-dependent variable. The potential interaction between amputation and diabetes was assessed.

Effect estimates were adjusted for age, gender, dialysis modality, amputation at baseline, smoking, blood pressure, body mass index, myocardial infarction or stroke in multivariable models. Analyses were performed with SPSS statistical software, version 20.0 (Armonk, NY: IBM Corp). Time dependent analyses were performed in stata version 14.1, (Statacorp, College Station, TX, USA).

Results

Patient characteristics

Between January 1997 and January 2007, 2051 patients who started renal replacement therapy were included in NECOSAD. Twenty five percent of patients had diabetes mellitus at baseline (Table 1). Sixty four percent of diabetic patients were treated with insulin injections therapy. Patients with diabetes were older (mean age 63, ± SD 13 years) compared to non-diabetics (59, ± SD 16). Fourty –six percent of diabetic patients had retinopathy for which laser coagulation was performed. Seventy- one percent of patients with diabetes had diabetes as primary renal disease.

Hemodialysis was the dialysis modality in 68% of patients with DM and 63% in patients without DM. The prevalence of cardiovascular morbidity at baseline was higher compared to patients without diabetes mellitus. Peripheral artery disease was present in 19% of patients with diabetes mellitus compared to 10 % in patients without diabetes mellitus.

Amputation

At baseline, 24 of 413 diabetic patients (5.8%) had an amputation compared to only 9 out of 1553 non-diabetic patients (0.5%) (Table 2). During follow up (mean duration 2.9, ± SD 2.3 years), 50 diabetic patients had a new amputation (12.1%), compared to 20 non-diabetic patients (1.2%). Amputation rates/ 1000 person years were respectively 47.9 (95% CI 36.3- 63.2) and 4.1 (95% CI 2.7-6.4) for diabetic patients and non-diabetic patients. The level of amputation was different in both groups; patients with diabetes had mainly minor amputations (5.1%), while patients without diabetes had mainly major extremity amputations amputations (0.6%). After a first amputation on dialysis therapy almost fifty percent of patients (24 out of 50) with diabetes had a second amputation compared to 20 % percent (5 out of 20) of patients without DM. The majority of patients (37/50 diabetic patients with an amputation) used insulin therapy.

Table 1. Baseline characteristics, patients with diabetes compared to patients without diabetes.

	Patients with diabetes (N=413)	**Patients without diabetes (N=1638)**
Age at start dialysis	63 (13)	59 (16)
Male gender (%)	55	64
Primary renal disease		
Diabetes Mellitus	295 (71%)	0
Glomerulonephritis	7 (2 %)	245 (15 %)
Renal Vascular disease	46 (11 %)	309 (19 %)
All other	65 (16%)	1084 (66 %)
Treatment modality (% HD)	68	63
Comorbidity (%)		
Cerebrovascular accident	13	6
Myocardial infarction	18	10
Severity of DM		
Peripheral artery disease without amputation (%)	19	10
Duration of DM (years)	16 (11)	0
Retinopathy (% lasercoagulation)	46	0
Insulin dependency (%)	64	0
Medication (%)		
Antihypertensive agents	85	70
Lipid lowering medication	34	18
Smoking (currently or recently quit)(%)	20	29
Blood pressure		
Systolic	153 (24)	148 (24)
Diastolic	79 (12)	84 (13)
Body Mass Index (kg/m2)	27 (5)	25 (4)
Laboratory values		
Cholesterol (mmol/l)	4.9 (1.4)	5.1 (1.3)
Haemoglobin (g/dl)	11.1 (1.6)	11.2 (1.6)
Calcium (mmol/l)	2.3(0.26)	2.4 (0.25)
Phosphate (mmo/l)	1.8 (0.53)	1.8 (0.55)
rGFR (ml/min per 1.73 m2)	5.6 (3.5)	5.2 (3.6)

Continuous predictors are presented as means (SD); categorical variables are presented as %.

Abbreviations: BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HD, hemodialysis; rGFR, residual glomerular filtration rate.

Table 2. Data on amputations.

	Patients with diabetes (N=413)	Patients without diabetes (N=1638)
First amputation		
Baseline	24 (5.8 %)	9 (0.6 %)
During follow up	50 (12.1 %)	20 (1.2 %)
Level of amputation (during follow up)		
Toe (minor)	21 (5.1%)	6 (0.4 %)
Feet (minor)	8 (1.9 %)	1 (0.06%)
Below knee (major)	16 (3.9 %)	9 (0.6 %)
Above knee (major)	5 (1.2 %)	4 (0.2 %)
Amputation rate/1000 person years	47.9	4.1
Days to incident amputation (mean, min-max)	511 (380)	671 (409)
Second amputation	24	5
Days to second ampuation (from first amputation) (mean, min-max)	88 (91)	139 (148)

Survival after amputation

In total 911 patients (44 %) died during follow-up. Fifty-four out of 70 patients with a first amputation during dialysis therapy died (77.1%). Four patients with an amputation and diabetes mellitus received a renal transplant compared to no transplants in patients with an amputation without diabetes mellitus. Other reasons for censoring during follow-up (moving to other center, center stopped participation, other and refusal) were similar in both groups.

Survival after amputation and diabetes status

Mortality was higher in patients with diabetes (HR 1.6 , 95 % CI 1.4-1.9) compared to non-diabetic patients adjusted for age, gender, amputation at baseline and dialysis modality. Amputation increased mortality risk more than fourfold, in patients without diabetes (HR 4.6, 95 % CI 2.8-7.6) as well as in patients with diabetes the (HR 4.6 95% CI 3.3-6.4), (figure 1). Further adjustment for smoking, blood pressure, body mass

index, myocardial infarction or stroke, did not change these results substantially (table 3). No formal interaction between diabetes and amputation was found (p=0.12 from likelihood ratio test) meaning that mortality risk after amputation is high but coexisting diabetes mellitus does not add further to this risk.

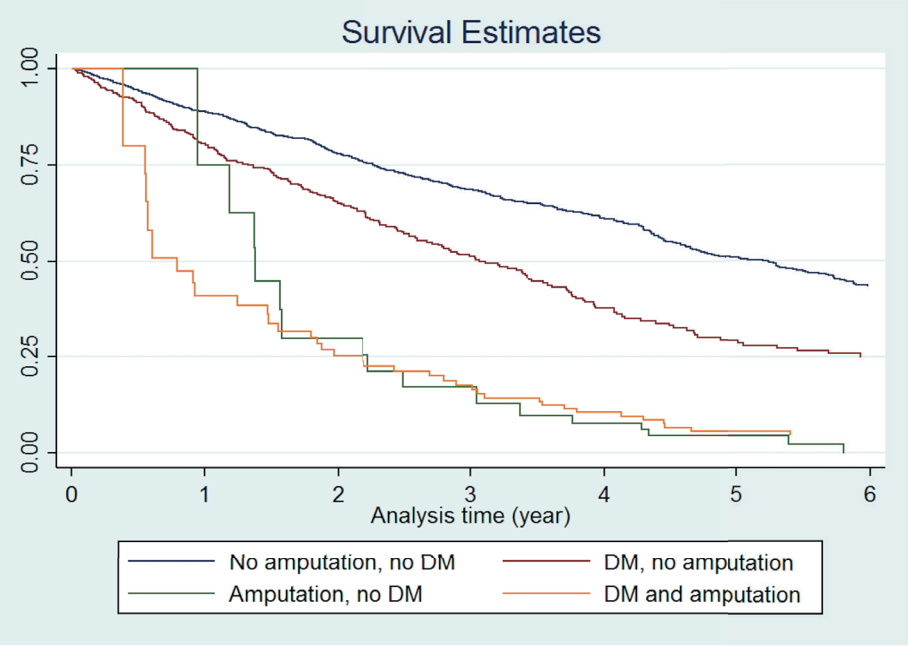

Figure 1. Survival without amputation and after amputation in diabetic and non-diabetic patients.

Table 3. Poisson regression: effect of incident amputation and diabetes mellitus on mortality in ESRD.

Patient group	N=	Crude HR (95% CI)	Adjusted HR (95% CI)a	Adjusted HR (95 % CI)b
1. amputation-, DM-	1618	1.0 (reference)	1.0 (reference)	1.0 (reference)
2. amputation-, DM+	363	1.7 (1.5, 2.0)	1.6 (1.4, 1.9)	1.6 (1.4, 1.9)
3. amputation+, DM-	20	5.9 (3.6, 9.8)	4.6 (2.8, 7.6)	4.6 (2.8, 7.5)
4. amputation+, DM +	50	3.9 (2.8, 5.5)	4.6 (3.2, 6.4)	5.0 (3.5, 7.2)

a. Model adjusted for age, gender, amputation at baseline
b. Model adjusted for age, gender, amputation at baseline, dialysis modality, smoking, blood pressure, body mass index, myocardial infarction or stroke

In a subanalysis in patients with a major amputation we found no difference in mortality risk in diabetic patients compared with non-diabetic patients. The number of patients with a minor amputation without diabetes mellitus was too small to perform a subanalysis in patients with a minor amputation.

Discussion

The results of this study demonstrate that the burden of non-traumatic amputation in dialysis patients remains high especially in patients with diabetes, with an incidence rate of amputation of 4/100 person years in diabetic patients compared with 0.4/100 person years in non-diabetic patients. We also showed that amputation in this medically compromised patient group is associated with a clearly increased mortality risk; this mortality risk was similar for diabetic and non-diabetic patients.

Survival among dialysis patients with diabetes mellitus is inferior to survival of non-diabetic dialysis patients[18-21], probably due to higher prevalence of diabetes related co-morbid conditions such as foot ulceration and infection, neuropathy, peripheral vascular disease and cardiovascular morbidity. These co-morbid conditions may also contribute to a higher incidence of amputation in diabetic dialysis patients. One could hypothesize that these co-morbid conditions also contribute to a decreased survival after amputation in dialysis patients with diabetes compared to non-diabetic patients. However results of this study showed that mortality after amputation in dialysis patients is high and diabetes mellitus does not further increase this mortality risk.

Hoffstad et al showed that mortality risk after lower extremity amputation in a large population with diabetes mellitus but without severe chronic kidney disease was threefold increased. They also showed that some of this risk excess can be explained by well-known complications of diabetes[22]. The study and also our results suggest that patients with an amputation have a poor prognosis, mostly independent of co-existing conditions such as diabetes, hypertension and presence of cardiovascular disease.

Furthermore the risk of a recurrent amputation in this study was high, especially in patients with diabetes mellitus. Almost 50 % of diabetic patients received a recurrent amputation during follow up, which is in line with data from studies on diabetic patients without ESRD[23, 24]. The number of patients who received a recurrent

amputation however was relatively small in the present study and these results further confirmation in independent cohorts with long term follow up.

There are some potential limitations that should be taken into account when interpreting the data. First, data on glycaemic control were not available. However, data on duration of diabetes mellitus, retinopathy for which laser coagulation therapy was performed and insulin dependency was available, which also reflects severity of diabetes. As the patients in the NECOSAD cohort are treated to prevailing diabetes guidelines, it is unlikely that glycaemic control is structurally different from control in other dialysis based cohorts. Similar reasoning applies to cardiovascular risk management. We thus consider our results generalizable to other dialysis based cohorts.

Second, severity of peripheral vascular disease and information about limb salvage therapy was not available. Third, by the design of the study, data on amputations were extracted from data on hospitalizations and surgery. Therefore we cannot exclude that some patients with a minor amputation without hospitalization were not included in this study. Another limitation of this study, due to inadequate sample size, is that we could not evaluate the number of patients in each subgroup of level of amputation, especially in the subgroup with minor amputations.

Although it is important to assess survival after amputation, from a patient's perspective it is also relevant to know what quality of life will remain after amputation. Only a few studies explored quality of life and/or functional outcomes after amputation on chronic dialysis therapy and reported a longer length of stay in hospital[25] and lower functional independence measure scores after limb amputation compared to patients without ESRD[26, 27]**.** Furthermore quality of life is reduced[28, 29]. This shows that the combination of ESRD and amputation poses a high disease burden on patients.

In order to reduce the number of amputations in dialysis patients further optimizing and/or implementing foot care according to the international guideline in the renal clinic is essential[30]. Patients with ESRD are often dialyzed in a renal care unit separate from the diabetes care unit, in which regular foot screening and foot care education might be suboptimal. Implementation of monthly foot checks in renal care units was associated with reduction of major lower limb amputations in diabetic incident hemodialysis patients[31].

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CHAPTER 7

General discussion

Patients with diabetes mellitus have the highest mortality risk within the dialysis population[1-4]. The presence of chronic kidney disease (CKD) in patients with diabetes is also strongly related to impaired quality of life[5, 6]. Research is warranted to prevent progressive diabetic kidney disease, improve quality of life and reduce mortality in this vulnerable population. In order to improve survival, more knowledge about which patients have the highest mortality risk and which risk factors and co-morbid conditions contribute to this increased mortality risk is essential. Whether intensifying treatment of risk factors and/or co-morbid conditions will improve health related outcomes should be investigated in future intervention trials. In this thesis research focused on several aspects of survival in diabetic dialysis patients. Furthermore we assessed different measures of glucose metabolism and their association with kidney function, among a Dutch sample of middle-aged adults in participants with normoglycemia, pre-DM, DM and newly diagnosed DM.

In **chapter 2** we assessed many different measures of glucose metabolism and their association with kidney function among Dutch middle-aged adults. Of the total participants (N= 6338), 54.6 % participants were classified as normoglycemic (reference), 34.8 % as pre-diabetes, 6.9 % as diabetes mellitus and 3.8 % as newly diagnosed diabetes mellitus. Diagnosed and newly diagnosed DM was associated with a higher eGFR, respectively + 2.1 ml/min/ 1.73 m^2 (95% CI -0.19, 4.4) and + 2.7 ml/ min/ 1.73 m^2 (95% CI -0.3, 5.7). The observed increase in eGFR in patients with (newly) diagnosed DM likely reflects hyperfiltration. Glomerular hyperfiltration in diabetes is established as an early manifestation of diabetic kidney nephropathy and may contribute to nephropathy progression and GFR decline[7-9]. Also we showed that the presence of micro-albuminuria is increasing from normoglycemia (1.4 %), pre-DM (3.5 %), diagnosed DM (6.2 %) to undiagnosed DM (8.3 %). Compared to other studies[10, 11], we found a relatively low occurrence of chronic kidney disease in this Dutch cross study population, which might be related to good metabolic control. This was reflected by a small number of patients with insulin use and a low prevalence of diabetic complications.

Furthermore we showed that both fasting and post-prandial glucose and HOMA-B, but not insulin resistance, were associated with glomerular hyperfiltration, while fasting glucose was also associated with micro-albuminuria. This implies that hyperinsulinemia is not associated with a first increase in eGFR (hyperfiltration) but is associated with a decline in eGFR.

In **chapter three** we compared survival of dialysis patients with diabetes mellitus as underlying cause of the renal failure versus dialysis patients with diabetes mellitus as co-morbid condition only. Also, mortality rates in these two groups were compared to mortality rates in dialysis patients without diabetes mellitus. Our hypothesis was that in patients with diabetic nephropathy, organ damage, such as retinopathy, neuropathy and cardiovascular complications, may be more severe in patients with diabetes as primary renal disease compared to patients with diabetes as a co-morbid condition. We assumed that patients with diabetes as primary renal disease might have more pronounced multisystem involvement and therefore have worse survival compared to patients with diabetes as a-comorbid condition on top of another primary renal disease.

Data for this study were collected from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter, prospective cohort study in which new patients with end stage renal disease (ESRD) were monitored until transplantation or death. Fifteen percent of the patients had diabetes as primary renal disease (N=281); 6 % had diabetes as co-morbid condition (N=107) and 79 % had no diabetes (N=1465). During follow-up, 42 % of patients (N=787) died. Compared to non-diabetic patients, mortality risk was increased for both patients with diabetes as primary renal disease and for patients with diabetes as co-morbid condition. Mortality was not higher in patients with diabetes as primary renal disease compared to patients with diabetes as co-morbid condition (HR 1.06; 95 % CI 0.79, 1.43). This study result was not in line with our primary hypothesis. Possible explanations may be the small sample size or the combination of two severe diseases (DM and ESRD) which both contribute to impaired survival and survival is not further affected by the subtype of DM.

To gain statistical power, we conducted a new study using a larger, international European cohort of dialysis patients. Data were used from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry. In this registry data on comorbidity were available from 7 different European countries. Results are described in **chapter 4**. In this study 3,624 patients (24%) had diabetes as primary cause of their renal disease and 1,193 (11%) had diabetes as a co-morbid condition whereas the majority had no diabetes (n=10,602). During follow-up, 7,584 (49%) patients died. In both groups of diabetic patients mortality was higher compared with the non-diabetic patients. Mortality was higher in patients with diabetes as primary renal disease than in patients with diabetes as a co-morbid

condition, adjusted for age, sex, country and malignancy (HR 1.20, 95% CI 1.10, 1.30). This suggests that, according to our hypothesis, in patients with diabetes as primary renal disease, diabetic complications are more severe and therefore have worse survival compared to patients with diabetes as a-comorbid condition.

In **chapter 5** we aimed to develop a prediction model for 1-year mortality in diabetic dialysis patients. Data were used from NECOSAD. A total of 394 patients were available for statistical analysis; 82 (21%) patients died within one year after baseline (defined as 3 months after starting dialysis therapy). The final prediction model contained seven predictors; age, smoking, history of macrovascular complications, duration of diabetes mellitus, Karnofsky scale, serum albumin and hemoglobin level. Discrimination of the model was good, as shown by the c-statistic of 0.810. Internal validation based on bootstrapping showed a slightly lower, but still adequate performance (c-statistic 0.790). In addition, calibration was also good (calibration slope after bootstrapping 0.903). Sensitivity analyses showed stability of results. Before however implementing the model in clinical practice, for example for counselling patients regarding their prognosis, external validation is needed, as prediction models sometimes fail to be validated.

In **chapter 6** we compared survival after amputation in diabetic dialysis patients to non-diabetic dialysis patients. Data were collected from NECOSAD. At baseline, 24 of 413 diabetic patients (5.8%) had an amputation compared to only 9 out of 1553 non-diabetic patients (0.5%). While on dialysis, amputation risk was clearly higher in diabetic patients: 50 of 413 diabetic patients had a new amputation (12.1 %), compared to 20 of 1553 non-diabetic patients (1.2 %). In line, amputation rates/ 1000 person years were about 10 times higher for diabetic patients compared to non-diabetic patients. Amputation increased mortality risk more than fourfold in patients without diabetes as well as in patients with diabetes mellitus. We concluded that the incidence of amputation in diabetic dialysis patients is high and is accompanied by a high mortality risk independent of diabetes status.

Future perspectives

Clinical consequences

1. Mortality in the diabetic dialysis population

Life expectancy of the diabetic dialysis population remains poor, with an estimated mortality risk of 30-106/ 1000 patients years[12]. One and five year survival were respectively 87.8 % and 50.6 % stratified for age and gender[13]. One central hypothesis of this thesis was that mortality risk was modified by whether diabetes was the cause of the renal disease or whether it was merely a co-morbid condition. The idea was that patients with diabetes as primary renal disease might have more severe diabetic complications and therefore have worse survival compared to patients with diabetes as a-comorbid condition and a non-diabetic cause of ERSD. Indeed, in a large multicentre study we showed that mortality was higher in patients with diabetes as primary renal disease compared with those with diabetes as a co-morbid condition[4].

When comparing dialysis patients with type 1 DM to patients with type 2 DM, the highest mortality is shown in patients with diabetes type 1[14, 15]. Compared with nondiabetic patients, the adjusted hazard ratio (HR) for death was 1.64 ($P < 0.0001$) in type 1 diabetes and 1.13 ($P < 0.0001$) in type 2 diabetes[14]. When starting dialysis, patients with type 1 DM often have a longer duration of diabetes mellitus and may have more severe complications and/or co-morbid conditions compared with patients with type 2 DM. Also in patients with diabetes as primary renal disease we postulated that complications and comorbidities may be more severe compared to patients with diabetes as a co-morbid condition. This raises the question whether patients with diabetes as primary renal disease often might have underlying DM type 1. This is an important consideration as most large registry based studies with ESRD patients do not differentiate the two diabetes subtypes. Therefore we performed additional analysis in which we differentiated the patients with diabetes as primary renal disease by type 1 and type 2 diabetes and showed a higher mortality in patients with type 1 diabetes (HR 1.45, 95 % CI 1.30, 1.61)[4]. Furthermore mortality in patients with type 1 or type 2 diabetes as primary renal disease was higher compared with patients with diabetes (type1 or 2) as a co-morbid condition, with HR of 1.62 (95 % CI 1.44, 1.82) and 1.12 (95% CI 1.03, 1.22) respectively. This suggests that differences

in the underlying pattern of diabetes (type 1 or type 2) cannot fully account for the difference in mortality found between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition.

Renal registries for patients with ESRD often have no differentiation between the subtype of DM and the primary cause of ESRD (diabetes as primary renal disease or as a co-morbid condition) while there is an important difference in mortality between the subgroups of diabetic patients[12]. For a better registration and evaluation of clinical outcomes from data from these registers, we suggest to include the subtype of diabetes and the primary cause of renal disease.

2. Towards personalized medicine in patients with DM in dialysis care

Doctors implicitly take the prognosis of patients into account when formulating treatment goals. In diabetic patients with a relatively better life expectancy the treatment goals for metabolic control might be more stringent in order to prevent further complications compared to patients with a reduced life expectancy[16]. For example patients who are on a waiting list for (pancreas) kidney transplantation have a better survival compared to patients who are not admitted to a waiting list[17]. These patients might therefore benefit from a more stringent glycemic control in order to prevent further complications during pre-transplantation period. However this improved glycaemic control has to be balanced against the increased risk of (severe) hypoglycemia. Furthermore, patients with ESRD and DM have a broad spectrum of diabetic complications and co-morbid conditions like diabetic cardiomyopathy, depression and cognitive impairment. Therefore, management of diabetic dialysis patients should involve not only focus on the kidney and diabetes, but also on prevention, early detection and effective treatment of all diabetic complications and co-morbid conditions. This emphasizes the need for individualized treatment goals in diabetic dialysis patients, in which health care providers together with their patients assess personal goals based on patients preferences, co-morbid conditions and life expectancy To prioritize treatment goals, we suggest to first evaluate patients life expectancy, with a better life expectancy for patients admitted on a waiting list for kidney (pancreas) transplantation compared to those who are not admitted. Second, assess patients preferences and treatment goals. Third, prevent further severe diabetic complications such as diabetic feet and blindness through referral to a specialized team for diabetic foot care and the ophthalmologist.

3. Optimizing pre-dialysis care

Prior to initiate dialysis therapy, early and repeated shared decision-making conversations, between health care providers, patients, and their families about the potential advantages and disadvantages of dialysis therapy should consider each patient's unique goals and priorities. A prediction model which predicts 1-year mortality in diabetic dialysis patients might be a helpful tool in these shared decision-making conversations. This model should contain parameters prior to initiating dialysis treatment. We showed that it is possible to make such a prediction model, in this case for (chronic) diabetic incident dialysis patients, which includes specific diabetes-related patient characteristics and co-morbid conditions[18]. This prediction model included parameters that are easily to obtain (age, smoking, Karnofsky scale for example) which makes this prediction model useful for clinical practice. It is important to know that for some patients the estimated mortality risk can be as high as 70 %.

It has been shown that nephrologist's care for more than one year prior to initiating dialysis is more frequent in patients with diabetes as a co-morbid condition compared to patients with diabetes as primary renal disease (53.5% and 46.4%, respectively)[19]. Importantly, late referral of patients with chronic kidney disease to a nephrologist is associated with reduced survival[20-22]. This emphasises the need for early and optimal pre-dialysis care in patients with diabetes as primary renal disease. As many patients with diabetes as primary renal disease are treated by endocrinologists and not by nephrologists, a closer collaboration could further optimize treatment for dialysis patients with diabetes mellitus. Furthermore higher mean HbA1C (≥64 mmol/mol) over the 1-year pre-ESRD transition period, was associated with higher 1-year post-ESRD mortality (adjusted HRs 1.19 [95% CI 1.07-1.32] compared to the reference group HbA1C (< 64 mmol/mol) suggesting that better pre-ESRD glycemic control might improve survival on dialysis[23].

Areas of uncertainty and future directions of research

1. Hypoglycemia and reduced impaired awareness of hypoglycaemia in diabetic dialysis patients

In a large multicentre study, we showed that mortality was higher in patients with diabetes as primary renal disease compared with those with diabetes as a co-

morbid condition[4]. This difference in mortality rates may be related to several factors. First it could be explained by differences in prevalence and severity of diabetic complications. In patients with diabetes as primary renal disease, diabetic complications are more severe and therefore have worse survival compared to patients with diabetes as a-comorbid condition and less severe complications. Second, there might be a difference in nephrologist care prior to initiating dialysis as discussed above. Furthermore, it might be explained by differences in prevalence and/or consequences of (severe) hypoglycaemia. Recurrent hypoglycemia reduces symptomatic and hormonal responses to subsequent hypoglycemia, which is associated with impaired awareness of hypoglycemia (IAH)[24, 25]. Patients with ESRD may be even more vulnerable to hypoglycemia due to impaired clearance of antihyperglycemic medication and co-existing conditions such as malnutrition or neuropathy. Furthermore, in patients with diabetes as primary renal disease, diabetic complications are not limited to the kidney but likely involve multisystem complications, including autonomic neuropathy and impaired awareness of hypoglycemia and this may be more pronounced in patients with diabetes as primary renal disease compared to patients with diabetes as a comorbid condition. However to the author's knowledge the prevalence of IAH in diabetic dialysis patients is unknown. In patients with type 1 DM without ESRD, IAH induces a sixfold higher risk of severe hypoglycemia, which is defined as episodes in which the help of others was needed[26]. This contributes to substantial morbidity and mortality[27].

There has been sparse investigations of risk factors and consequences of (severe) hypoglycemia in patients with DM on dialysis therapy. Also in our studies information on (severe) hypoglycemia was lacking; not surprising as hypoglycemia is often not well recorded. One study showed a dose-dependent relationship between increasing frequency of hypoglycaemia-related hospitalizations and higher mortality risk after transitioning to dialysis therapy, such that experiencing 3 or more events in the pre-ESRD prelude period was associated with 2-fold higher mortality risk on dialysis [28]. Another cohort study showed that in patients on dialysis, the occurrence of hypoglycaemia (defined as a serum glucose level < 2.8 mmol/l), appeared to be a life-threatening complication as 27 % of patients died within two days of the onset of hypoglycaemia[29]. In this study, mortality was also increased in hypoglycaemic patients without known diabetes mellitus, reflecting that hypoglycaemia is a symptom of severe illness.

2. Glycemic target in diabetic dialysis patients

If hypoglycaemia is indeed associated with higher mortality rates in dialysis patients, a less stringent glycemic goal can be considered. Unfortunately, the optimal glycemic target in diabetic dialysis patients is unknown. A general conservative glycemic target for patients with co-existing conditions is a HbA1c level of < 8.0% (64 mmol/mol) [16, 30]. Glycated hemoglobin (HbA1c) is the standard marker to assess glycemic control and provides information about mean glucose levels over the previous 2 to 3 months. However, HbA1c values are affected by factors as anemia, erythrocyte turnover, reduced erythrocyte survival or an increase in young erythrocytes during erythropoietin-stimulating agents (ESA) treatment; this means that in dialysis patients HbA1c levels appear not to be an optimal marker of glycemic status and may inaccurately reflect long term glycemic control in patients with renal diseases[31, 32].In patients without ESRD HbA1c levels above > 53 mmol/mol (> 7 %) are clearly associated with an increased risk in mortality[33, 34]. However, in diabetic dialysis patients it is unclear whether HbA1c values are related to mortality. Some studies show an positive relation between HbA1c values and mortality[35-39] and other studies show no association between HbA1c values and mortality[40-42]. This may also reflect that HbA1c is not an adequate measurement of long term glycemic control in dialysis patients.

Fructosamine is an alternative glycemic index that has a shorter half-life than HbA1c, and thus, reflects recent (i.e. 1–3 weeks) glycemic status. It primarily originates from the non-enzymatic glycation of albumin (~90%), as well as other proteins[43]. A disadvantage of fructosamine is the interference of low molecular weight substances (i.e. urea and uric acid) [44]. These low molecular substances are increased in dialysis patients and elevate fructosamin concentrations. Albumin-corrected fructosamine levels were reported to correlate better than HbA1c with hospitalization and infection in diabetic patients on hemodialysis[45], but the prognostic role of fructosamine in predicting mortality in hemodialysis patients is unknown.

Glycated albumin (GA) is a ketoamine formed from a non-enzymatic oxidation of albumin by glucose. GA is another alternative glycemic marker which has been shown to be more accurate for the assessment of glycemic control than glycated hemoglobin in diabetic dialysis patients[46-48]. Similar to fructosamine, GA reflects the glycemic status over the preceding 2–3 weeks. However nephrotic-range proteinuria

decreased GA values independent of glycemic state[49]. Therefore in patients with overt proteinuria, GA is not the ideal marker for the assessment of glycemic control. Elevated glycated albumin is associated with coronary artery stenosis[50, 51]. However also data about the prognostic role of GA in predicting mortality, or as a variable that can be used to target therapy, in dialysis patients are lacking.

Currently, continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) may provide the most accurate and reliable information about glucose control during a longer time period in diabetic dialysis patients. A small study, including 15 patients using CGM for 6 weeks, showed that CGM monitoring was associated with more frequent treatment changes and better glucose control, without increased risk of hypoglycemia[52]. However, studies with a larger sample size and longer follow up time in a dialysis population are needed. Unfortunately, these systems are expensive and thus far only available for a minority of patients, only for patients who are treated with basal bolus insulin injection therapy. When these systems will become less expensive in the future, more patients can use them. Another advantage of CGM is an alarm function during early stages of a hypoglycemia which might reduce the frequency of severe hypoglycemia in diabetic dialysis patients. Furthermore most patients experience an improved quality of life, however some patients experience a loss of quality of life due to a higher psychological burden of these devices[53].

3. Future perspectives

In the upcoming years, an annual increase of ~ 3% in the prevalence of patients with DM and ESRD is predicted[54]. Data from a Dutch registry showed an annual decrease in renal replacement therapy in type 1 diabetes and an annual increase in type 2 diabetic nephropathy over the last decade[55]. This could be explained by the current increased prevalence in patients with type 2 DM in the Netherlands. The observed decrease in renal replacement therapy in type 1 diabetes might be explained by better treatment, earlier surveillance for proteinuria and an earlier start of renoprotective medications. However there are many questions which still have to be resolved for optimizing treatment in patients with ESRD and DM. How to prevent complications, reduce mortality and improve quality of life? Recent trials have shown promising results in patients with DM and mild CKD (eGFR > 30 ml/min/ 1.73 m^2) with treatment with sodium glucose transporter 2 inhibitors (SGLT2-i) which resulted in a risk reduction of about 40 % of developing ESRD/ doubling creatinine levels[56-60].

It would be of interest to investigate if treatment with SGLT2-i (probably in a higher dose) is also effective in preventing ESRD in patients with more severe nephropathy, especially in patients with CKD class 4 (eGFR ≥ 15 en < 30 ml/min/ 1.73 m^2). From a clinical perspective, we advise a closer collaboration between nephrologists and endocrinologist to optimize (pre-) dialysis care: in pre-dialysis care to optimize the trajectory to initiate dialysis therapy or transplantation on time; during dialysis therapy to optimize glycemic control and screen for complications (eg adequate diabetic foot control) and thereby prevent further clinical complications such as visual loss and/or amputations. From a scientific perspective we suggest that future research might focus on the impact and prevention of (severe) hypoglycemia in diabetic dialysis patients. We also recommend the use of a glucose sensor (continuous or intermittent) in the treatment of every dialysis patient with diabetes mellitus. Glucose sensor measurements from days to weeks reflect glucose control and is not affected by erythrocyte lifespan, in contrast to HbA1c. Further research is needed to determine upon which degree of glucose control, expressed as a percentage of time within (target) range, is associated with complications and mortality risks specifically for a dialysis population.

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CHAPTER 8

Nederlandse samenvatting
List of publications
Dankwoord
Curriculum vitae

Nederlandse samenvatting

Ongeveer 20-40 % van de patiënten met Diabetes Mellitus (DM) ontwikkelen chronische nierschade (CKD, Chronic Kidney Disease)[1-3]. Chronische nierschade wordt ingedeeld in 5 categorieën waarbij categorie 1 milde nierschade betreft en categorie 5 eind stadium nierfalen (ESRD, End stage Renal Disease) dit houdt in dat nierfunctie vervangende therapie, dialyse, noodzakelijk is[4]. Binnen de dialysepopulatie hebben patiënten met diabetes mellitus (DM) het hoogste mortaliteitsrisico[5-8]. Daarnaast is in patiënten met DM en chronische nierziekte de kwaliteit van leven sterk verminderd[9, 10]. Er is meer onderzoek nodig in deze kwetsbare populatie met DM en CKD naar het verbeteren van de kwaliteit van leven, het verbeteren van de overleving en indien nierschade optreedt het voorkomen van verdere progressie van nierschade. Om de overleving te verbeteren, is het essentieel om meer kennis te verkrijgen over welke patiënten het hoogste mortaliteitsrisico hebben en welke risicofactoren en co-morbide aandoeningen bijdragen aan dit verhoogde mortaliteitsrisico. Toekomstige interventiestudies moeten uitwijzen of een intensievere behandeling van risicofactoren en /of co-morbide aandoeningen de overleving van patiënten met DM en ESRD zal verbeteren. In dit proefschrift is het onderzoek gericht op verschillende aspecten van overleving bij dialysepatiënten met DM. Verder hebben we de associatie tussen verschillende maten van glucosemetabolisme en hun verband met de nierfunctie beoordeeld in een groep Nederlandse volwassenen van middelbare leeftijd.

In **hoofdstuk 2** hebben we verschillende maten van glucosemetabolisme en hun verband met de nierfunctie onderzocht in Nederlandse volwassenen van middelbare leeftijd. Data werden verkregen uit de NEO (Nederlandse Epidemiologie en Obesitas) studie, een prospectieve cohort studie, opgezet om de verschillende mechanismen die leiden tot obesitas gerelateerde ziekten te onderzoeken. Het merendeel van deelnemers in deze studie had overgewicht of obesitas. Van de totale deelnemers (N = 6338) werden 54,6% deelnemers geclassificeerd als normoglycemisch (referentie), 34,8% als pre-diabetes, 6,9% als diabetes mellitus en 3,8% als nieuw gediagnosticeerde diabetes mellitus. Gediagnosticeerde en nieuw gediagnosticeerde DM was geassocieerd met een hogere eGFR, respectievelijk + 2,1 ml / min / 1,73 m2 (95% BI -0,19, 4,4) en + 2,7 ml / min / 1,73 m2 (95% BI -0,3, 5,7). De toename van eGFR bij patiënten met (nieuw) gediagnosticeerde DM reflecteert hyperfiltratie. Deze

glomerulaire hyperfiltratie in patiënten met DM is een uiting van vroege nierschade en kan bijdragen aan de progressie van nefropathie en nierfunctie achteruitgang[11-13].

Daarnaast toonden we aan dat de prevalentie van micro-albuminurie toeneemt bij gestoord glucosemetabolisme. De prevalentie was het laagst bij normoglykemie (1,4%), en nam toe bij gestoord glucose metabolisme: pre-DM (3,5%), gediagnosticeerde DM (6,2%) tot niet-gediagnosticeerde DM (8,3%). In vergelijking met andere studies[14, 15] vonden we een relatief laag voorkomen van chronische nierziekte in deze Nederlandse populatie, mogelijk een uiting van goede metabole controle. Dit werd weerspiegeld door een klein aantal patiënten met het gebruik van insuline en een lage prevalentie van DM-gerelateerde complicaties. Daarnaast toonden we aan dat zowel nuchtere als postprandiale glucose en HOMA-B, maar niet insuline-resistentie, geassocieerd waren met glomerulaire hyperfiltratie. Dit houdt in dat insuline resistentie niet geassocieerd is met een initiële toename in filtratie, (eGFR, een toename in eGFR wordt hyperfiltratie genoemd), maar geassocieerd is met een daling in nierfunctie.

In **hoofdstuk drie** hebben we de overleving vergeleken van dialysepatiënten met DM als oorzaak van nierfalen versus dialysepatiënten die DM hadden als co-morbiditeit, maar door een andere oorzaak dan DM, nierfalen hebben ontwikkeld. De overleving in deze twee groepen werd vergeleken met de overleving van dialysepatiënten zonder diabetes mellitus. Onze hypothese was dat bij patiënten met diabetische nefropathie, orgaanschade, zoals retinopathie, neuropathie en cardiovasculaire complicaties vaker voorkomen. En daarnaast dat de ernst van de complicaties meer uitgesproken is in patiënten met diabetes als primaire nierziekte in vergelijking met patiënten met diabetes als co-morbiditeit. Daarom veronderstelden wij dat patiënten met diabetes als primaire nierziekte een slechtere overleving hebben in vergelijking met patiënten met diabetes als co-morbiditeit.

Gegevens voor dit onderzoek werd verzameld uit de Nederlandse coöperatieve studie naar het uitvoeren van dialyse (NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis), een multicenter, prospectief cohortonderzoek waarin nieuwe patiënten met eindstadium nierziekte (ESRD) werden gevolgd tot transplantatie of overlijden. Vijftien procent van de patiënten had diabetes als primaire nierziekte (N = 281); 6% had diabetes als co-morbiditeit (N = 107) en 79% had geen diabetes mellitus (N = 1465). Tijdens de follow-up overleed 42% van de patiënten (N = 787). In vergelijking met patiënten zonder DM was de kans op overlijden verhoogd voor zowel

patiënten met diabetes als primaire nierziekte als voor patiënten met diabetes als co-morbiditeit. De mortaliteit was niet hoger in patiënten met diabetes als primaire nierziekte in vergelijking met patiënten met diabetes als co-morbiditeit (HR 1,06; 95% betrouwbaarheidsinterval (BI) 0,79, 1,43). Dit resultaat was tegenstrijdig met onze primaire hypothese. Mogelijke verklaring kan zijn de kleine steekproefgrootte. Een andere verklaring kan zijn dat een combinatie van twee ernstige ziekten (DM en ESRD) beiden bijdragen aan een verminderde overleving en de overleving niet verder wordt beïnvloed door het subtype DM; DM als co-morbiditeit of als primaire nierziekte.

Om onze hypothese in ander, groter, cohort te toetsen, hebben we een nieuwe studie uitgevoerd met behulp van een groter, internationaal Europees cohort van dialysepatiënten. Gegevens werden verkregen uit het register van de European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). In dit register waren gegevens over co-morbiditeit beschikbaar, waaronder gegevens uit 7 verschillende Europese landen. De resultaten worden beschreven in **hoofdstuk 4**. In deze studie hadden 3.624 patiënten (24%) diabetes als primaire oorzaak van hun nierziekte en hadden 1.193 (11%) diabetes als co-morbiditeit, terwijl de meerderheid geen diabetes had (n =10.602). Tijdens de follow-up overleden 7.584 (49%) patiënten. In beide groepen patiënten met DM was de mortaliteit hoger in vergelijking met patiënten zonder DM. De mortaliteit was hoger in patiënten met diabetes als primaire nierziekte in vergelijking met patiënten met diabetes als co-morbiditeit, gecorrigeerd voor leeftijd, geslacht, land en maligniteit (HR 1,20, 95% BI 1,10, 1,30). De effectschatter van deze studie in de ERA-EDTA database (1,20), is compatibel met het betrouwbaarheidsinterval van de studie in NECOSAD. Dit suggereert dat, in overeenstemming met onze hypothese, in patiënten met diabetes als primaire nierziekte, complicaties meer uitgesproken zijn en daarom een slechtere overleving hebben dan patiënten met diabetes als co-morbiditeit.

In **hoofdstuk 5** hebben we een statistisch model ontwikkeld dat de 1-jaars mortaliteit voorspeld in dialysepatiënten met DM op basis van gegevens uit de NECOSAD database. In totaal waren 394 patiënten beschikbaar voor statistische analyse; 82 (21%) patiënten overleden binnen een jaar na aanvang (gedefinieerd als 3 maanden na start van dialyse). Het uiteindelijke model bevatte zeven voorspellers; leeftijd, roken, geschiedenis van macrovasculaire complicaties, duur van diabetes mellitus, Karnofsky-schaal, serum albumine en hemoglobine. Voordat het model in de klinische praktijk wordt geïmplementeerd, bijvoorbeeld om patiënten te informeren over

hun prognose, is externe validatie noodzakelijk. Dat wil zeggen dat het model eerst getest moet worden in een andere patiëntenpopulatie waarbij geverifiëerd wordt of de resultaten in een andere populatie in overeenstemming zijn met de resultaten die wij beschreven hebben in de studie. We concludeerden op basis van diverse statistische analyses dat de interne validatie (validatie binnen de eigen studie) goed was. De discriminatie van het model, weergegeven door de c-statistiek, was 0.810, dat wil zeggen dat de voorspelling van het model in 0.810 van de gevallen overeen komt met de daadwerkelijke uitkomst.

In **hoofdstuk 6** hebben we de overleving na amputatie in dialysepatiënten met DM vergeleken met dialysepatiënten zonder DM. Gegevens uit de NECOSAD database werden verzameld. Bij aanvang van de studie hadden 24 van de 413 patiënten met DM (5,8%) een amputatie vergeleken met slechts 9 van de 1553 patiënten zonder DM (0,5%). Tijdens dialyse was het risico op amputatie duidelijk hoger in patiënten met DM: 50 van de 413 patiënten met DM hadden een nieuwe amputatie (12,1%), vergeleken met 20 van de 1553 patiënten zonder DM (1,2%). Het aantal amputaties/ 1000 persoonsjaren was ongeveer 10 keer hoger voor patiënten met DM in vergelijking met patiënten zonder DM. Amputatie verhoogde het risico op overlijden meer dan vier keer bij zowel patiënten zonder diabetes als bij patiënten met diabetes mellitus. Wij concludeerden dat de incidentie van amputatie bij dialysepatiënten met DM hoog is en gepaard gaat met een hoog risico op overlijden onafhankelijk van de aan - of afwezigheid van DM.

Toekomstige ontwikkelingen

Klinische implicaties

1. Sterfte in de dialysepopulatie met DM

De levensverwachting van de dialysepopulatie met DM blijft slecht, met een geschat risico op overlijden van 30-106 / 1000 patiënt jaren[16]. Een -, en vijf-jaars overleving zijn respectievelijk 87.8 % en 50.6 % gestratificeerd voor leeftijd en geslacht[17]. Een centrale hypothese van dit proefschrift was dat het risico op overlijden verschilt in patiënten waarvan DM de oorzaak was van nierfalen versus diabetes als co-morbiditeit en een andere oorzaak van nierfalen (niet DM gerelateerd). Het idee was dat patiënten met diabetes als primaire nierziekte mogelijk meer en ernstigere

complicaties hebben en daarom een slechtere overleving hebben in vergelijking met patiënten met diabetes als een co-morbiditeit. In een groot multicenteronderzoek hebben we inderdaad aangetoond dat de mortaliteit hoger was bij patiënten met diabetes als primaire nierziekte dan bij patiënten met diabetes als co-morbiditeit[8].

Wanneer de mortaliteit van dialysepatiënten met type 1 DM wordt vergeleken met type 2 DM, wordt de hoogste mortaliteit beschreven in patiënten met DM type 1 [18, 19]. In vergelijking met patiënten zonder DM is de gecorrigeerde hazard ratio (HR) voor overlijden 1,64 bij type 1 DM en 1,13 bij type 2 DM [18]. Bij het starten van dialyse hebben patiënten met type 1 DM vaak een langer duur van DM en mogelijk ernstigere complicaties en /of overige aandoeningen in vergelijking met DM type 2. Ook bij patiënten met diabetes als primaire nierziekte veronderstellen we dat complicaties en overige aandoeningen ernstiger zijn in vergelijking met patiënten met diabetes als co-morbiditeit. Alhoewel we in onze studie geen verschil vonden in complicaties tussen patiënten met DM als primaire nierziekte en co-morbiditeit, moet wel rekening gehouden worden met het feit dat patiënten met DM als primaire nierziekte ongeveer 5 jaar jonger waren. Dit roept de vraag op of patiënten met diabetes als primaire nierziekte vaak een onderliggende DM-type 1 hebben. Dit is een belangrijke overweging, aangezien de meeste grote, op registratie gebaseerde onderzoeken met ESRD-patiënten geen onderscheid maken tussen de twee diabetes-subtypen. Daarom werd een aanvullende analyse uitgevoerd waarin we de patiënten met diabetes als primaire nierziekte hebben gedifferentieerd naar type 1 en type 2 diabetes (zie hoofdstuk 4) en een hogere mortaliteit aantoonden in patiënten met DM type 1 (HR 1,45, 95% BI 1,30, 1,61) [4]. Bovendien was de mortaliteit in patiënten met type 1 of type 2 diabetes als primaire nierziekte hoger in vergelijking met patiënten met diabetes (type 1 of 2) als co-morbiditeit, met HR's van respectievelijk van 1,62 (95% BI 1,44, 1,82) en 1,12 (95 % CI 1,03, 1,22). Dit suggereert dat verschillen in het onderliggende subtype DM (type 1 of type 2) niet volledig het verschil in mortaliteit kunnen verklaren tussen patiënten met diabetes als primaire nierziekte en patiënten met diabetes als co-morbiditeit.

In registraties van patiënten met ESRD wordt vaak geen onderscheid gemaakt in het subtype DM en tevens wordt vaak de primaire oorzaak van ESRD (diabetes als primaire nierziekte of als comorbiditeit) niet genoteerd, terwijl er een belangrijk verschil in mortaliteit is tussen de diverse subgroepen[16]. Om een betere registratie en evaluatie van klinische resultaten te verkrijgen van gegevens uit deze

registers, adviseren wij het subtype diabetes en de primaire oorzaak van nierfalen (nauwkeuriger) te registreren.

2. Naar gepersonaliseerde zorg voor patiënten met DM en ESRD

Artsen houden impliciet rekening met de prognose van patiënten bij het formuleren van behandeldoelen. In patiënten met DM en een relatief goede levensverwachting kunnen de behandeldoelen voor metabole controle en bloeddruk strenger zijn om verdere complicaties te voorkomen; dit kan anders zijn bij patiënten met een slechtere levensverwachting[20]. Bijvoorbeeld patiënten die op een wachtlijst staan voor nier (pancreas) transplantatie hebben een betere overleving in vergelijking met patiënten die niet op een wachtlijst staan[21]. Deze patiënten kunnen daarom baat hebben bij een striktere glucose controle om verdere complicaties tijdens de pre-transplantatieperiode te voorkomen. Deze verbeterde glucose controle moet echter worden afgewogen tegen het verhoogde risico op (ernstige) hypoglykemie. Bovendien hebben patiënten met ESRD en DM vaak ernstige complicaties en overige aandoeningen zoals diabetische cardiomyopathie, depressie en cognitieve stoornissen[9]. Daarom moet de behandeling van patiënten met DM niet alleen gericht zijn op de nierfunctie en glucose controle, maar ook op preventie, vroege detectie en effectieve behandeling van alle complicaties en overige aandoeningen. Dit benadrukt de behoefte aan geïndividualiseerde behandeldoelen in patiënten met DM, waarbij zorgverleners samen met hun patiënten persoonlijke behandeldoelen opstellen op basis van de voorkeuren van de patiënt, overige aandoeningen en levensverwachting. Om de behandeldoelen te prioriteren, stellen wij voor om eerst de levensverwachting van de patiënt goed in kaart te brengen. Ten tweede, evalueer de voorkeuren van patiënten en maak persoonlijke behandeldoelen. Ten derde, voorkom verdere ernstige complicaties zoals diabetische voet en blindheid door verwijzing naar een gespecialiseerd team voor diabetische voetzorg en de oogarts.

3. Optimalisatie van pre-dialysezorg

Voorafgaand aan het initiëren van dialyse, vinden bij voorkeur ruim op tijd, herhaalde gedeelde besluitvormingsgesprekken plaats tussen zorgverleners, patiënten en hun families over de potentiële voor- en nadelen van dialyse waarbij rekening gehouden wordt met de unieke persoonlijke doelen en prioriteiten van elke patiënt. Een model dat de 1-jaars mortaliteit in dialyse patiënten met DM voorspelt, kan een

nuttig hulpmiddel zijn in deze gedeelde besluitvorming. In onze studie hebben we aangetoond dat het mogelijk is om een dergelijk voorspelmodel te maken, in dit geval voor (chronische) patiënten met DM, met specifieke diabetes gerelateerde patiëntkenmerken[22]. Dit voorspelmodel bevat parameters die gemakkelijk te verkrijgen zijn (bijvoorbeeld leeftijd, roken, Karnofsky-schaal) en daarom toepasbaar is in de klinische praktijk. Het is belangrijk om te weten dat voor sommige patiënten het geschatte risico op overlijden kan oplopen tot 70%.

Er is aangetoond dat de zorg van de nefroloog, wat standaard zou moeten zijn, gedurende meer dan een jaar voorafgaand aan het starten van dialyse vaker voorkomt bij patiënten met diabetes als comorbiditeit in vergelijking met patiënten met diabetes als primaire nierziekte (respectievelijk 53,5% en 46,4%)[23], alhoewel beide percentages relatief laag zijn. Late verwijzing van patiënten met een chronische nierziekte naar een nefroloog is geassocieerd met verminderde overleving[24-26]. Dit benadrukt de relevantie aan vroege en optimale pre-dialysezorg bij patiënten met diabetes als primaire nierziekte. Aangezien veel patiënten met diabetes als primaire nierziekte worden behandeld door endocrinologen en niet door nefrologen, zou een nauwere samenwerking de behandeling voor dialyse patiënten met DM verder kunnen optimaliseren. Verder was een hogere gemiddelde HbA1C waarde (≥64 mmol/ mol) gedurende het jaar voorafgaand aan start van dialyse geassocieerd met een hogere mortaliteit op 1 jaar na start van dialyse (HR's 1,19 [95% BI 1,07-1,32] in vergelijking met de referentiegroep HbA1C (<64 mmol/ mol). Dit suggereert dat een betere glucose controle voor start dialyse de overleving na start dialyse, zou kunnen verbeteren[27].

Kennis lacunes en richting van toekomstig onderzoek

1. Hypoglykemie en verminderd gevoel van hypoglykemie (impaired awareness) in dialyse patiënten met DM

In een groot multicenter onderzoek hebben we aangetoond dat de mortaliteit hoger was in patiënten met diabetes als primaire nierziekte in vergelijking met patiënten met diabetes als co-morbiditeit[8]. Dit verschil in mortaliteit kan verklaard worden door verschillende factoren. Ten eerste door verschillen in prevalentie en ernst van complicaties tgv DM. Ten tweede kan er een verschil zijn in de zorg door een nefroloog (wel of niet tijdig gestart) voorafgaand aan start van dialyse, zoals hierboven besproken.

Daarnaast zou het kunnen worden verklaard door verschillen in prevalentie en /of gevolgen van (ernstige) hypoglykemie. Recidiverende hypoglykemieën verminderen de symptomatische en hormonale reacties op daaropvolgende hypoglykemieën, en dit kan gepaard gaan met een verminderd gevoel van hypoglykemie (impaired awareness of hypoglycemia, IAH)[28, 29]. Patiënten met ESRD kunnen nog kwetsbaarder zijn voor (gevolgen van) een hypoglykemie als gevolg van verminderde klaring van glucose verlagende medicatie en daarnaast overige aandoeningen zoals ondervoeding of neuropathie. Bovendien zijn complicaties ten gevolge van diabetes niet beperkt tot de nier, maar omvatten ze waarschijnlijk multisysteem complicaties, waaronder autonome neuropathie en verminderd gevoel van hypoglykemie en dit kan meer uitgesproken zijn bij patiënten met diabetes als primaire nierziekte in vergelijking met patiënten met diabetes als co-morbiditeit. De prevalentie van IAH in dialysepatiënten met DM is niet uitgebreid onderzocht. Bij patiënten met type 1 DM zonder ESRD induceert IAH een zesvoudig hoger risico op ernstige hypoglykemie, dat wordt gedefinieerd als episoden waarbij de hulp van anderen nodig was[30]. Dit draagt bij tot substantiële morbiditeit en mortaliteit[31].

Er is weinig onderzoek gedaan naar risicofactoren en de gevolgen van (ernstige) hypoglykemie bij patiënten met DM die dialysetherapie ondergaan. Ook ontbrak in onze studies informatie over (ernstige) hypoglykemie; dit is niet verwonderlijk omdat hypoglykemie vaak niet goed wordt geregistreerd. Eén studie toonde een relatie aan tussen de frequentie van hypoglykemie-gerelateerde ziekenhuisopnames en een hoger sterfterisico na start van dialyse, waarbij 3 of meer gebeurtenissen in de pre- dialyse periode was geassocieerd met een 2-maal hoger risico op overlijden na start dialyse[32]. Een ander cohortonderzoek toonde aan dat het optreden van hypoglykemie (gedefinieerd als een serum glucose waarde <2,8 mmol/ l) bij dialysepatiënten een levensbedreigende complicatie leek te zijn, aangezien 27% van de patiënten overleed binnen twee dagen na het begin van hypoglykemie[33]. In deze studie was de mortaliteit ook verhoogd in patiënten met een hypoglycemie zonder bekende diabetes mellitus, wat erop wijst dat hypoglykemie een symptoom is van ernstige ziekte.

2. Glucose streefwaarden in dialysepatiënten met DM

Indien hypoglykemie inderdaad geassocieerd is met een hogere mortaliteit in dialysepatiënten met DM, moeten mogelijk minder stringente glucose streefwaarden

worden overwogen. Helaas zijn de optimale glucose streefwaarden en tijd binnen deze glucose streefwaarden in dialysepatiënten met DM niet bekend. Een algemeen behandeldoel in patiënten met DM met co-morbiditeit is een HbA1c-niveau van <8,0% (64 mmol/ mol)[20, 34]. Geglyceerd hemoglobine (HbA1c) is de standaard marker om de mate van glucose controle te beoordelen en geeft globaal informatie over de gemiddelde glucosewaarden van de voorgaande 2 tot 3 maanden. HbA1c-waarden worden echter beïnvloed door factoren als bloedarmoede, verminderde overleving van erytrocyten of een toename van jonge erytrocyten tijdens de behandeling met erytropoëtine-stimulerende middelen (EPO). Dit betekent dat in dialysepatiënten de HbA1c-waarden geen optimale marker voor de mate van glucose controle is, en mogelijk een onnauwkeurige weerspiegeling van de mate van glucose controle op lange termijn[35, 36]. In patiënten zonder eindstadium nierfalen zijn HbA1c-waarden boven> 53 mmol/ mol (> 7%) duidelijk geassocieerd met een verhoogd risico op sterfte[37, 38]. In dialysepatiënten met DM is het echter onduidelijk of HbA1c-waarden verband houden met mortaliteit. Sommige studies tonen een associatie aan tussen HbA1c-waarden en mortaliteit[39-43] en andere studies tonen geen verband aan tussen HbA1c-waarden en mortaliteit[44-46]. Hierbij dient te worden opgemerkt dat het HbA1c als gemiddelde waarde een weerspiegeling van zowel te hoge als te lage glucosewaardes is.

Fructosamine is een alternatief voor HbA1c als maat voor glucoregulatie. Echter fructosamine heeft een kortere halfwaardetijd in vergelijking met HbA1c en weerspiegelt dus de recente (1-3 weken) mate van glycemische controle. Het is voornamelijk afkomstig van een niet-enzymatische glycatie van albumine (~ 90%), evenals andere eiwitten[47]. Een nadeel van fructosamine is de interferentie van stoffen met een laag molecuulgewicht (d.w.z. ureum en urinezuur)[48]. Deze laagmoleculaire stoffen zijn verhoogd bij dialysepatiënten en verhogen de fructosamine concentraties. Voor albumine gecorrigeerde fructosamine-waarden bleken beter dan HbA1c te correleren met ziekenhuisopname en infectie in patiënten met DM die hemodialyseerden[49], maar de prognostische rol van fructosamine bij het voorspellen van mortaliteit bij hemodialysepatiënten is niet bekend.

Geglyceerd albumine (GA) is een ketoamine gevormd uit een niet-enzymatische oxidatie van albumine door glucose. GA is een andere alternatieve glycemische marker waarvan is aangetoond dat deze nauwkeuriger is voor de beoordeling van glycemische controle dan HbA1c in dialysepatiënten met DM[50-52]. Net als

fructosamine weerspiegelt GA de glycemische status van de voorgaande 2-3 weken. Proteïnurie in de nefrotische range (verlies van eiwit in de urine van 3 gram of meer per dag) verminderd echter GA-waarden onafhankelijk van de glycemische instelling[53]. Daarom is GA in patiënten met overte proteïnurie niet de ideale marker voor de beoordeling van de glycemische controle. Verhoogd geglyceerd albumine wordt geassocieerd met coronairstenose[54, 55]. Er ontbreken echter ook gegevens over de prognostische rol van GA bij het voorspellen van mortaliteit. Daarnaast worden fructosamine en geglyceerd albumine niet in elk laboratorium bepaald.

Momenteel kan met behulp van op sensor gebaseerde technologie, zoals de continue glucosemonitoring (CGM) of flash-glucosemonitoring (FGM), de meest accurate en betrouwbare informatie geven over de mate van glucose controle. Een kleine studie, waarin 15 patiënten gedurende 6 weken CGM gebruikten, toonde aan dat CGM-monitoring was geassocieerd met frequentere veranderingen in behandeling en daarnaast een betere glucosecontrole, zonder verhoogd risico op hypoglykemie [56]. Echter studies met een grotere steekproefomvang en langere follow-up duur zijn nodig in de dialyse populatie. Helaas zijn deze systemen kostbaar en tot nu toe slechts beschikbaar voor een minderheid van patiënten, namelijk voor patiënten die behandeld worden met insuline therapie middels basaal bolus schema. Wanneer deze systemen in de toekomst mogelijk goedkoper worden, kunnen meer patiënten er gebruik van maken. Een ander voordeel van CGM is een alarmfunctie tijdens vroege stadia van hypoglykemie die de frequentie van ernstige hypoglykemie in dialysepatiënten met DM zou kunnen verminderen. Bovendien ervaren de meeste patiënten een verbeterde kwaliteit van leven, maar sommige patiënten ervaren een verlies van kwaliteit van leven als gevolg van een hogere psychologische belasting van deze apparaten[57].

3. Perspectieven voor de toekomst

De voorspelling is dat in de komende jaren de prevalentie van patiënten met DM en ESRD verder toeneemt met een jaarlijkse stijging van 3.2 %[58]. Een Nederlandse studie rapporteerde een daling in het aantal patiënten met ESRD door type 1 DM, maar een stijging van ESRD door type 2 DM[59]. De stijging van patiënten met ESRD en type 2 DM zou verklaard kunnen worden door de toename van het totale aantal patiënten met DM2[60]. De daling van het aantal patiënten met ESRD en type 1DM zou onder andere verklaard kunnen worden door beter onderzoek van

proteïnurie en het vroeger starten van nierprotectieve medicatie. Er zijn veel vragen die nog moeten worden opgelost om de behandeling voor patiënten met ESRD en DM te optimaliseren. Hoe kunnen we complicaties voorkomen, sterfte verminderen en de kwaliteit van leven verbeteren, zoals het beter herkennen en ondersteunen bij depressieve klachten? Wat betreft de medicamenteuze behandeling hebben onderzoeken met SGLT2 (natrium glucose transporter 2) remmers zeer goede resultaten getoond in het voorkomen van nierfunctie achteruitgang in patiënten met een verminderde nierfunctie (eGFR < 30 ml/min/ 1.73 m^2). Met deze middelen wordt het risico op dialyse/ en of verdubbeling van de eGFR met ongeveer 40 % verlaagd [61-65]. Het zou heel interessant zijn om te onderzoeken of deze middelen (bijvoorbeeld in een hogere dosering) ook effectief zijn in patiënten met een al slechtere nierfunctie (eGFR ≥ 15 en < 30 ml/min/ 1.73 m^2).

Vanuit een klinisch perspectief adviseren we een nauwere samenwerking tussen nefrologen en endocrinologen om (pre-) dialysezorg te optimaliseren: in pre-dialysezorg om het traject te optimaliseren om dialysetherapie of transplantatie op tijd te initiëren; tijdens dialyse om de glucose controle te optimaliseren en te screenen op complicaties (bijvoorbeeld adequate voetcontrole) en daarmee verdere klinische complicaties zoals visusverlies en/of amputaties te voorkomen. Vanuit wetenschappelijk perspectief suggereren we dat toekomstig onderzoek zich zou kunnen richten op de impact en preventie van (ernstige) hypoglykemie in dialysepatiënten met DM. Verder raden we aan om een glucosesensor (continu of intermitterend) in te kunnen zetten in de behandeling van iedere dialyse patiënt met diabetes mellitus. Glucose sensormetingen worden niet beïnvloed door de levensduur van de erythrocyt, zoals de HbA1c waarde. Verder onderzoek is nodig naar het effect van glucoseregulatie, dit wordt met behulp van een sensor weergegeven middels een percentage van de tijd binnen het (doel)bereik, en de associatie met complicaties en sterfte risico's specifiek voor de dialyse populatie.

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Curriculum Vitae

Mariëlle Schroijen werd geboren op 23 Oktober 1979. Na het behalen van haar atheneum diploma aan het Revius Lyceum te Doorn, begon zij in 1998 haar studie geneeskunde aan de Universiteit van Leiden. In 2002 deed zij onderzoek in het St. Elisabeth Hospitaal, Willemstad, Curaçao: naar T-celaktiviteit bij sikkelcelziekte. Zij behaalde haar arts examen in 2005. In 2006 begon zij aan de opleiding interne geneeskunde in het Haga ziekenhuis, Den Haag (opleider R.M. Valentijn) en vervolgde deze opleiding in het LUMC, Leiden (opleiders prof Dr. J.A. Romijn, prof Dr. J.T van Dissel). In 2010 trouwde zij met Pim van der Heiden, samen kregen zij twee dochters (Lotte 2010) en Sanne (2012). In 2013 registreerde zij zich als internist-endocrinoloog (opleider J.W.A. Smit). Sinds 2013 is zij staflid van de afdeling endocrinologie en combineerde opleiding, klinische werkzaamheden met het onderzoek zoals beschreven in dit proefschrift. In 2017 nam zij deel aan de stuurgroep MODY (maturity onset diabetes of the young) en in 2018 organiseerde zij samen met E.J.P de Koning het 1e Leidse MODY congres in Nederland. Sinds 2018 is zij chèf de poli van de endocrinologie.