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

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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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