Progression of CKD form pre-dialysis : natural course, risk factors, and outcomes

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Chapter 1 |

Introduction, aim, and outline of this thesis

Introduction

Chronic kidney disease (CKD) is a severe condition, characterized by an abnormal urinary protein excretion and/or impaired kidney function due to kidney damage. The prevalence of CKD in the Netherlands is 11%.[1] Furthermore, worldwide the prevalence and incidence of CKD are increasing.[2-4] CKD develops as a result of an underlying primary kidney disease, such as diabetes mellitus, glomerulonephritis, or renal vascular disease.[5] The primary kidney disease causes fibrosis and sclerosis of the functional kidney units, the glomeruli, that leads to impaired kidney function.[6] Usually, kidney function is expressed by the glomerular filtration rate (GFR). The GFR is the flow rate of filtered fluid through the kidney corrected for the body surface area (mL/min/1.73m^2). In healthy persons, the GFR is typically larger than 90 mL/min/1.73m^2, while in patients with severely impaired kidney function the GFR may even be below 10 to 15 mL/min/1.73m^2.[7] Decreased GFR has been associated with complications in virtually all organ systems, such as the cardiovascular system, bone, skin, lungs, and the central nervous system. Important symptoms for these complications include hypertension, anemia, accelerated atherosclerosis, mineral bone disease, malnutrition, and neuropathy.[7] Furthermore, patients with impaired kidney function are at increased all-cause mortality risk[8;9] and especially cardiovascular mortality is shown to be increased in these patients.[10-12]

CKD progression

After the initial damage of the kidney, a series of adaptive changes takes place in the kidney ('adaptive glomerular hyperfiltration'), which is first sufficient to adapt to the initial kidney damage, but finally causes destruction of the remaining functional kidney tissue.[5] This destructive process is often mediated by comorbidities like hypertension and proteinuria.[6] Hence, CKD frequently shows a progressive course. Obviously, in the ideal situation patients are identified at the earliest stages of CKD to allow early medical intervention or behavioral changes. Population wide screening or screening a subset of high risk patients for the presence of CKD therefore seems the solution to detect patients when they are in the pre-clinical phase. However, the quest for a suitable and valid screening test for CKD detection turns out to be hard and the ideal test has not been found yet.[13] Consequently, many patients are only identified when their GFR is severely impaired and symptoms start to develop, which is usually when the GFR has dropped below 30 mL/min/1.73m^2. CKD may progress until end-stage renal disease develops and renal replacement therapy, which is either kidney transplantation or dialysis treatment, is needed to survive. Fortunately, therapeutic interventions aimed at treating the primary kidney disease and at strictly controlling the comorbidities early in the course of CKD are shown to be effective in slowing or preventing the progression towards end-stage renal disease.[6;14-17]

Treatment guidelines

Since adequate management of CKD patients is associated with the progression rate of their disease, guidelines have been developed to improve the delivery of care in these patients. For example, in 2003 the National Kidney Foundation Disease Outcomes Quality Initiative (NKF

KDOQI) guidelines have been introduced,[18] while in 2009 the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have been established.[19] Both guideline series are based on clinical evidence and expert opinion. The KDIGO guidelines however, build on more recent evidence and are therefore intended and recommended to replace the KDOQI guidelines. In the Netherlands, CKD patients are recommended to be treated according to the guidelines of the Dutch Federation of Nephrology (NfN),[20] which are based on both the KDOQI and KDIGO guidelines. The clinical practical guidelines include suggestions for the treatment of complications of kidney dysfunction, like hypertension, hyperphosphatemia, and anemia, and also provide suggestions for preparation for renal replacement therapy.

Multidisciplinary pre-dialysis care

Ideal preparation for renal replacement therapy comprises of referral to a multidisciplinary team, consisting of a nephrologist, a dietician, and a social worker. The nephrologist is responsible for management of the kidney disease for example by combating the presence of uremic symptoms, and medication prescription, while the dietician is involved in dietary counseling, for example with respect to protein and salt restriction. It is the social workers duty to provide the patient with practical support when requested. For example help with filling out forms. This multidisciplinary approach strives for adequate control of CKD progression, preparation of vascular access for dialysis treatment, and guidance with regard to diet, lifestyle, and smoking cessation.[21] An important aspect of the multidisciplinary approach is that patients are provided with extensive information about their disease and possible treatment strategies, which enables them to make deliberate decisions on their therapy. In order to get as optimal pre-dialysis care as possible, timely referral to a multidisciplinary team is essential. Sometimes a distinction is made between 'late referral', defined as referral at or less than three months prior to the start of renal replacement therapy, and 'early referral', defined as referral more than one year prior to the start of renal replacement therapy. Late referral has been associated with increased morbidity and mortality after initiation of renal replacement therapy.[22-24] Causes of late referral may be either physician related (e.g. due to poor communication between the treating physician and the nephrologist), patient related (e.g. lifestyle or social economic factors), or just unavoidable (e.g. a very slowly progressing disease that remains unnoticed for a long period).[22;25] Important consequences of late referral include insufficient patient information, higher hospitalization rates, increased loss of kidney function, uremia, and increased mortality.

Aim and scope of this thesis

Management of patients on pre-dialysis care appears an important factor in improving outcomes of CKD patients with severely impaired kidney function. For that reason, efforts should be made to optimize multidisciplinary pre-dialysis care. The effects of pre-dialysis care on the level of GFR at start of dialysis may have important consequences even after the start of dialysis. Furthermore, other factors may play an important role in the progression of CKD. The aim of this

thesis is to study the progression of CKD from the phase of pre-dialysis care to the dialysis phase. More specifically, the following objectives are formulated:

a) To study the association between pre-dialytic risk factors (family history and serum phosphate and calcium levels) and disease progression during pre-dialysis care;
b) To study the association between a pre-dialytic risk factor (the duration of pre-dialysis care) and disease progression after the start of dialysis;
c) To study differences in outcomes (decline of kidney function and mortality) during pre-dialysis care and dialysis after the start of dialysis.

To that end, the thesis is divided into three parts; each part is concentrating on a different patient category: the first part addresses patients new on pre-dialysis care; the second part addresses patients in the transition period between pre-dialysis care and dialysis; the third part addresses patients new on dialysis.

Outline of this thesis

Methodological background

Clinical (epidemiological) studies are particularly suitable to study the effect of a risk factor on a particular outcome. To study whether an association between a risk factor and the outcome under study differs between specific sub-groups of patients, specific analytical tools are required. These analytical tools deserve extra attention and are therefore introduced separately in **Chapters 2** and **3**. These chapters describe specific epidemiological methods to measure interaction and how to report interaction within clinical studies. The methods thus described will be used later in this thesis.

Part 1: Pre-dialysis care

Chapter 4 presents a study that was performed in the PREPARE (PREdialysis PAtients REcords)-1 cohort, a retrospective Dutch cohort study in incident pre-dialysis patients. This study investigated whether a positive family history of diabetes, cardiovascular disease, and/or kidney disease is associated with disease progression, as measured by a faster decline of kidney function and increased mortality in the first year of pre-dialysis care.

It has been shown that pre-dialysis care is associated with prolonged survival, also after the start of dialysis; therefore it is important to focus on the treatment of patients during this pre-dialysis phase. As stated earlier, several guidelines for treatment of CKD patients exist. **Chapter 5** aims to describe whether patients are actually treated according to the recommended guidelines for mineral metabolism (serum phosphate and serum calcium) and whether achievement of these guidelines is associated with a prolonged dialysis-free survival during the first two years of pre-dialysis care. This analysis was performed in the prospective Dutch PREPARE-2 cohort, which includes incident pre-dialysis patients.

Part 2: From pre-dialysis care to the start of dialysis

Since mortality in dialysis patients is largely increased, we studied in a cohort of Dutch incident dialysis patients, the NECOSAD (NEtherlands COoperative Study on the Adequacy of Dialysis) study, whether patients who were treated by a nephrologist before the start of dialysis treatment (i.e. patients who were referred early) have a better survival during dialysis treatment as compared to patients who were referred late. We additionally studied whether high-risk populations such as diabetics and elderly (aged 70 years and above) have additional benefit of early referral. (**Chapter 6**) In addition to time of referral, other risk factors may play a role in the poor prognosis of dialysis patients, for example, the declining kidney function, which is an important characteristic of CKD. To study whether the pattern of decline of (residual) renal function attenuates after the initiation of dialysis treatment, we explored the decline of GFR in 1861 patients from the NECOSAD cohort in the year before until one year after the initiation of dialysis treatment (**Chapter 7**).

Part 3: Dialysis therapy

As outlined above, CKD is a severe condition that even with adequate treatment is associated with increased morbidity and mortality. The prevailing theory is that the increased mortality risk can be largely explained by an increased cardiovascular mortality risk. **Chapter 8** presents a comparison of the cardiovascular and non-cardiovascular mortality rates of dialysis patients with the mortality rates in the general population. This study was performed in a large database of European incident dialysis patients (ERA-EDTA Registry).

In **Chapter 9** the results presented in the previous chapters are summarized and discussed in a broader context, including the clinical implication of these results and suggestions for further research.

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