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Chapter 1

General introduction, aim, and outline of this dissertation
General introduction

Chronic kidney disease

Chronic kidney disease (CKD) is an illness that is characterized by the presence of persistent kidney damage and/or a glomerular filtration rate (GFR; a measure for kidney function) smaller than 60 mL/min/1.73 m² for three months or longer.\(^1\) CKD can be classified into five stages based on disease severity; Figure 1 depicts the stages of CKD according to the kidney damage and GFR. In CKD stage 5, the most advanced stage of CKD, many patients progress towards end-stage kidney disease (ESKD) in which kidney replacement therapy (i.e., transplantation or dialysis) becomes necessary to prolong life.\(^1\)

![Figure 1. Classification of CKD stages](image)

Causes of CKD

Our kidney function decreases when we get older; this decrease in kidney function starts around the age of forty, and thereafter declines with approximately 0.4 mL/min a year.\(^2\) On top of this natural aging of the kidneys, there are numerous factors that contribute to the development of CKD. Common causes for CKD include pyelonephritis (i.e., infection of the renal pelvis), inherited diseases (e.g., Alport syndrome or polycystic kidney disease), obstructions of the urinary tract (e.g., due to kidney stones, tumours or an enlarged prostate), glomerulonephritis (i.e., a group of diseases that cause inflammation and damage the part of the kidneys that filter blood),
hypertension and diabetes mellitus (DM), with hypertension and DM as leading underlying causes of CKD.\textsuperscript{3-6} Additionally, lifestyle factors such as smoking and obesity have been identified as risk factors for the development of CKD.\textsuperscript{5-7}

**Prevalence and incidence of CKD**

CKD is a major public health problem. The prevalence of CKD worldwide is estimated to be 8 to 16\%,\textsuperscript{5,8} and the estimated prevalence of CKD in the Netherlands ranges between 6.7 and 12\%.\textsuperscript{9,10} Furthermore, it is expected that the number of people with CKD will increase even further due to the aging population, and due to the global increase of weight excess and type 2 DM.\textsuperscript{11,12} For example, it is estimated that more than half of the adult population (aged 30 to 64 years, without CKD) in the United States will develop CKD during their lifetime.\textsuperscript{13}

**Disease progression of CKD**

The kidneys are responsible for various vital functions, including the regulation of the salt and fluid balance in the body, production of enzymes and hormones (e.g., to stimulate red blood cell production and to regulate blood pressure), regulation of the acidity of blood and the mineral balance of bones, and the removal of waste products from the blood. Consequently, when kidneys stop functioning properly, fluids and toxins build up in the body and various health complication arise such as hypertension, proteinuria (i.e., leakage of proteins into the urine), anaemia (i.e., decreased amount of red blood cells or haemoglobin [Hb] in the blood), weak bones, hyperkalaemia (i.e., increased potassium levels in the blood that influence heart functioning), nerve damage, and cardiovascular complications.\textsuperscript{4}

The rate at which CKD progresses varies widely among individuals: progression can range from almost no decline in kidney function to a fast decline (i.e., more than 5 mL/min/1.73 m\textsuperscript{2} per year), and in many patients the decline in kidney function does not follow a linear pattern, but a non-linear pattern that also includes periods of stable kidney function.\textsuperscript{14} This high degree of heterogeneity in disease progression can be partly explained by the various factors that play a role in the development and progression of CKD, including the cause of CKD, age, gender, ethnicity, level of protein excretion, blood pressure, history of cardiovascular disease (CVD), hyperglycaemia (i.e., glucose control in patients with DM), and lifestyle factors such as smoking, obesity and sodium [i.e., salt] intake.\textsuperscript{14-17}
Finally, as CKD progresses, the risk for mortality increases, and this risk for mortality is not limited to patients with ESKD; on the contrary: many patients with CKD do not progress towards ESKD but die before kidney replacement therapy is initiated. Although it is often hard to isolate the cause of death, various studies show that the commonly coexisting conditions anaemia, DM, and CVD are important risk factors for mortality in patients with CKD.

**Physical and mental burden of CKD**

CKD is a notoriously ‘silent disease’: in the earlier stages of CKD people are often unaware of the presence and/or progression of the disease, and many people do not experience CKD-related symptoms until approximately 30% of their kidney function is left. From this stage onward (i.e., CKD stage 3) patients experience an increase in overt symptoms, including nausea, sleep difficulties, itching, weight loss, fatigue, difficulties becoming sexually aroused, restless legs, muscle cramps, oedema, and breathlessness. Additionally, patients with CKD that also received the diagnosis DM and CVD often experience more symptoms compared to patients without such comorbidities.

The burden of CKD is not limited to the experience of bodily symptoms; the disease has a disruptive impact on many aspects of peoples’ lives, including their ability to work, social participation, and emotional well-being. Patients’ evaluation of health-related quality of life (HRQOL) is often used as an indication of the impact that a disease has on various life domains, and this evaluation includes the physical domain (e.g., physical [role] functioning) and the emotional domain (e.g., mental health and social role functioning). In patients with CKD, levels of HRQOL generally decrease as the disease progresses and the most severely compromised levels of physical and mental HRQOL are found in patients receiving dialysis treatment. However, compared to the general population, lower levels of physical and mental HRQOL are already reported by patients with moderately decreased kidney function and by patients receiving predialysis care (i.e., CKD stages 3 to 5). Especially the predialysis phase is often perceived as a stressful period during which patients experience an increase in bodily-symptom burden and medication side-effects, symptoms of anxiety and depression, and feelings of helplessness and hopelessness with the approaching need for kidney replacement therapy and an uncertain future. Furthermore, lower levels of HRQOL in patients receiving predialysis care have been associated with a faster progression towards ESKD and mortality.
Treatment of CKD

Nephrological care aims to slow down disease progression and optimize HRQOL in patients with CKD, and Dutch patients with CKD receive regular care according to the treatment guidelines of the Dutch Federation of Nephrology (guidelines that are partly based on the international Kidney Disease Outcomes Quality Initiative\(^1\) and Kidney Disease Improving Global Outcomes\(^{14}\) guidelines).\(^{37,38}\) This dissertation focuses on patients in the early stages of CKD (i.e., CKD stages 1 to 3) and on patients with advanced CKD who do not receive kidney replacement therapy (i.e., CKD stages 4 and 5; predialysis care) and a brief overview of regular treatment in both populations will be provided below.

*Treatment in CKD stages 1 to 3*

Most patients in CKD stage 1 to 3 are treated in the primary care setting by a general practitioner. Some patients in these earlier stages are referred to a specialist (i.e., a nephrologist or internist) in a medical centre, and this referral depends on the cause of CKD, the age of the patient, the rate of disease progression, and the presence of comorbid conditions. Regular care consists of visits to their physician once or twice a year during which kidney function, protein excretion, and other important parameters for the progression of CKD and comorbid conditions (e.g., blood pressure) is measured. If necessary, patients will receive pharmacotherapy, for example: Renin-Angiotensin-Aldosterone System (RAAS) blockade medication to reduce blood pressure and protein excretion.\(^{37,39}\)

Lifestyle modifications are also considered important in these earlier stages of CKD to slow down disease progression and to prevent cardiovascular complications. Therefore, patients with CKD often receive the advice to pursue a healthy lifestyle: to undertake regular physical exercise, limit alcohol intake, achieve or maintain a healthy weight, stop smoking and eat healthily (e.g., limit calorie, fat, and/or sodium intake).\(^{1,14,37,39}\) For many of these lifestyle recommendation, evidence showing that these modifications will indeed lead to improved health outcomes in patients with CKD is scarce, but increasingly studies do provide evidence for the beneficial effects of sodium reduction in patients with CKD. For instance, randomised crossover trials show that if patients with CKD reduce their sodium intake, blood pressure decreases\(^{40-43}\); this relationship between reduced sodium intake and decreased blood pressure has also been found in the general population,\(^{44,45}\) but blood pressure of patients with CKD is particularly sodium sensitive, and thus,
sodium reduction has an even more robust impact on blood pressure of patients with CKD. Moreover, a low-sodium diet reduces protein excretion, increases the efficacy of RAAS-blockade medication, and reduces the risk for cardiovascular complications and the progression towards ESKD. Therefore, limiting sodium intake has been identified as an important treatment strategy to maximize disease control in patients with CKD. In practice, this means that health care professionals advise patients with CKD to restrict their dietary sodium intake to a maximum of 2000 mg sodium a day (i.e., 5 grams of salt), that sodium excretion is measured and discussed during consultations, and that, if desired, patients receive nutritional counselling by a dietician. However, most patients with CKD do not succeed in adhering to the low-sodium diet: their sodium intake remains, despite the efforts of both patients and professionals, equal to the excessive sodium intake of the general population (9 - 12 g/day). It appears that current nephrological care does not provide the support that patients with CKD need to incorporate the sodium treatment guidelines into their daily life, and thus, implementation of additional support strategies into nephrological care is vital.

Treatment in CKD stages 4 and 5

When the kidney function drops below 30 mL/min/1.73 m², patients receive predialysis care in a medical centre by a multidisciplinary team consisting of a nephrologist, nurse practitioner, dietician, and social worker. Regular care consists of visits to the medical centre approximately every four months, and the frequency of these consultations can increase up to once a month in CKD stage 5. The aim of predialysis care partially overlaps with the aim of the treatment in CKD stages 1 to 3, namely to slow down disease progression and to prevent and treat health complications and comorbid conditions. However, due to the increased rate at which kidney function declines and the increased prevalence of cardiovascular events and metabolic complications (e.g., anaemia, hyperkalaemia and metabolic acidosis [i.e., excessive quantities of acid in the body]) in this advanced stage of the disease, the treatment is more intensive and complex: kidney function and other health parameters are monitored more frequently, patients receive more pharmacotherapy (e.g., erythropoietin stimulating agent (ESA) and/or iron supplements to treat anaemia), and patients receive additional lifestyle recommendations (e.g., protein, potassium and/or phosphate diet). If desired, support aimed at increasing adherence to the treatment guidelines can also be provided by the multidisciplinary team (e.g., nutritional counselling by a dietician or the support of a social worker to identify psychosocial problems related to treatment nonadherence).
Predialysis care also aims to prepare patients for the final stage of CKD, the ESKD phase. Patients receive information about the different ESKD treatment options: haemodialysis (i.e., the blood is purified outside the body using a dialysis machine), peritoneal dialysis (i.e., the blood is filtered using the patient’s peritoneum in the abdomen), kidney transplantation (i.e., receive a kidney from a living or deceased donor), or conservative treatment (i.e., palliative care). The most suitable option for an individual patient and the timing of the initiation of kidney replacement therapy depends on a combination of factors (e.g., life expectancy, physical and mental condition, history of peritonitis [i.e., an infection of the peritoneum], and living situation), and the personal preference of the patient and the physician.\textsuperscript{58,55} Often the preferred option is kidney transplantation because life expectancy and HRQOL is higher compared to other ESKD treatment options.\textsuperscript{56} However, not all patients are eligible for transplantation and, due to the shortage of available donor kidneys, patients spend on average as many as three years on the waiting list for a kidney transplant.\textsuperscript{57}

Finally, predialysis care not only aims to slow down disease progression but also to optimize HRQOL. However, the multidisciplinary treatment guidelines provide little guidance on how to monitor HRQOL or which strategies are effective to improve HRQOL. One treatment to improve HRQOL is described in more detail and that is the use of medication (i.e., ESA and/or iron supplements) in patient with anaemia.\textsuperscript{33,38} However, the management of anaemia in patients with CKD is complex and the optimal Hb level is still unknown: striving for high Hb levels (> 12 g/dL) by means of anaemia medication increases HRQOL,\textsuperscript{58} but concerns have also been raised about striving for such high Hb levels as it could also lead to adverse outcomes (e.g., increased risk for hypertension and cardiovascular events).\textsuperscript{59} Consequently, the treatment guidelines advise to strive for a narrow Hb target (≥ 11 to < 12 g/dL).\textsuperscript{33,38} Therefore, additional research about the effects of targeting high Hb levels using anaemia medication on HRQOL is warranted in order for professionals and patients to make well-informed treatment decisions. Furthermore, opportunities to improve HRQOL by means of non-medical strategies should be explored as well, and to this end, studies investigating the role of non-clinical factors (e.g., psychosocial factors) in outcomes among patients receiving predialysis care are required.
Chapter 1

Possibilities to improve nephrological care and theoretical perspectives

As pointed out in the previous sections, there are still possibilities to improve the support for patients with CKD, and to improve both disease progression and HRQOL prior to the ESKD phase. This dissertation aims to identify such opportunities by using three closely related perspectives: the biopsychosocial, patient-centred and self-regulation perspective. Before elaborating on the specific areas of nephrological care that will be further explored in this dissertation, an overview of the perspectives will be provided below.

Biopsychosocial perspective

In 1977, the psychiatrist George L. Engel published a paper titled “The need for a new medical model: a challenge for biomedicine”. In this paper, Engel states that the biomedical model, the scientific model that has guided modern Western medicine so far, has had a tremendous positive impact on the development of medicine, for instance the cure of acute infectious diseases. However, he criticizes its narrow biomedical focus leading clinicians to solely take into account the biological processes of a disease, thereby reducing patient’s illness to a set of physical symptoms and disregarding all other factors such as patients’ subjective experience and behaviours. Engel believes that, in order to adequately understand and respond to suffering, clinicians should take into account not just the biological domain but also the psychological and social domains, as they all contribute to illness and health. Therefore, he proposes a new scientific model that integrates all three domains, the biopsychosocial model, as a more holistic and humanistic approach to guide medicine.

The biopsychosocial model is a systems approach characterized by multiple interconnecting hierarchical levels with ‘person’ in the centre of the model (see Figure 2) – this latter system level reflects the patient and the patient’s experiences, and should be the starting point for each clinician. To evaluate the problems of a patient, the clinician should, in close cooperation with the patient, gather data on all levels by means of physical examinations, laboratory tests and conversations in order to adequately formulate and test hypotheses (i.e., construct a unique biopsychosocial model for each patient). Hereafter, a treatment plan is formulated by the clinician aimed at improving health and/or reducing distress of the patient, and if needed, this treatment plan includes a referral to other professionals (e.g., a psychologist). Engel proposes that the biospsychosocial model should be used as a framework for clinical practice, but also medical research and teaching.
The biopsychosocial model has been widely embraced and, worldwide, organizations have endorsed this approach (e.g., the World Health Organization and the American Psychiatry Association). Several changes can be observed since the introduction of this model, for example: psychosocial knowledge and skills are taught in medical
schools, integrated care clinics have emerged (e.g., psychosomatic or medical-psychiatry clinics), and there are many scholars that consider the biopsychosocial model as a framework for their research and practice, particularly in the field of health psychology.\textsuperscript{62-64}

Furthermore, numerous studies have also demonstrated the interaction between the biological, psychological and social domains, for instance: a great amount of evidence is acquired for the notion that psychological (e.g., depressive symptoms, stress, and illness perceptions), behavioural (e.g., lifestyle and coping behaviours), and social (e.g., social support) factors affect disease, illness and health.\textsuperscript{62-64} However, there are still opportunities to improve the implementation of this approach, for example in research (e.g., more interdisciplinary research combining clinical and psychosocial variables), and in clinical practice (e.g., the implementation of biopsychosocial research can be improved).\textsuperscript{62-65}

*Patient-centred perspective*

Patient-centred medicine was introduced in 1969 by the psychoanalyst Enid Balint as an alternative method for the dominant illness-oriented medical approach.\textsuperscript{66} Over the years, various definitions of patient-centred care have been proposed but there seems to be consensus on what the essence of patient-centred care is, namely: “care organized around the patient […] in which providers partner with patients and families to identify and satisfy the full range of patient needs and preferences” (Frampton et al., 2008, p. 4).\textsuperscript{67}

Furthermore, a comprehensive patient-centred framework is the framework of Stewart and colleagues which consists of the following six interconnecting domains (see Figure 3): (1) exploring both the disease and the illness experience (i.e., disease process and status, illness impact on daily functioning, and patients’ feelings, ideas about the illness, and expectations regarding treatment), (2) understanding the whole person (i.e., all aspects of patients’ lives; the biopsychosocial perspective), (3) finding common ground regarding management (i.e., defining the problem, treatment goals, and roles for both the patient and the clinician), (4) incorporation of prevention and health promotion (e.g., health enhancement and risk reduction), (5) enhancing the patient-doctor relationship (e.g., caring, trust and sharing of power), and (6) being realistic about limitations, teamwork and resources.\textsuperscript{68,69}
Since the late 1970s, the number of publications in which scholars argue that a more patient-centred medical care is needed increased rapidly, and influential organisations such as the Institute of Medicine and the World Health Organization identify patient-centred care as an important strategy to improve the quality of care in the 21st century.70,71 Furthermore, although it is difficult to draw one single conclusion regarding the effectiveness of patient-centred interventions (i.e., studies often define patient-centred care differently or include different intervention components), many studies demonstrate that patient-centred approaches can improve a broad range of outcomes (e.g., health and functional outcomes, well-being, self-care behaviours, patient-physician communication, and patient satisfaction with care), and can reduce the costs and use of health care services.72–75 Thus, patient-centred approaches appear promising to improve the quality of care, possibly also in a cost-effective way.

There are, however, still opportunities for improvement when it comes to the implementation of patient-centred approaches, also in nephrological care. For
instance, patients with CKD indicate that they desire a patient-centred approach in which professionals pay more attention to psychosocial aspects of living with CKD (e.g., coping with the disease and retaining an optimal quality of life) and in which additional support is provided to integrate self-management into their daily lives.\textsuperscript{24,76–79} Professionals involved in the care of patients with chronic conditions including CKD, also believe that patient-centred approaches (e.g., looking beyond biomedical aspects, addressing psychosocial issues, and including the patient-perspective) is important for high quality care, but acknowledge that such approaches are not fully part of regular care yet.\textsuperscript{80–82} One factor that may play a role in the implementation of patient-centred approaches in nephrological care is the available evidence: numerous studies show the importance of patient-centred approaches,\textsuperscript{72–75} but evidence for such approaches in patients with CKD, especially prior to ESKD, is limited.\textsuperscript{83}

\textit{Self-regulation perspective}

Self-regulation theory is a psychological framework that is often used for understanding and explaining health and illness behaviours.\textsuperscript{84–89} Various self-regulation frameworks have been developed over the years, and although each framework has its own theoretical approach, most self-regulation theories do share certain basic assumptions. Self-regulation is commonly referred to as “a systematic process of human behaviour that involves setting of personal goals and steering behaviour toward the achievement of established goals” (Zeidner, Boekaerts and Pintrich, 2000, p. 751).\textsuperscript{90}

Individuals are seen as active agents that strive to achieve goals within a changing environment, and the motivation to pursue these goals stems from a perceived discrepancy between individuals’ current state and a desired future state.\textsuperscript{85,86} This dynamic goal-process can be divided into three phases: a motivational phase (i.e., a phase of goal selection and setting), an action phase (i.e., a phase of active goal pursuit), and a maintenance phase (i.e., a phase of goal attainment, maintenance, or disengagement). In order to successfully go through these phases of behaviour change, both skills and cognitions play a crucial role, including anticipatory coping, self-monitoring, feedback, coping strategies, emotional control, and satisfaction with the new behaviour.\textsuperscript{85}
Another aspect that self-regulation theory considers to be important for behaviour change is goal ownership. Deci and Ryan suggest that goals are more likely to be achieved when people pursue goals that are self-chosen and personally important (i.e., autonomous regulation), and not if people feel coerced or pressured by external or internal forces (i.e., controlled regulation). Indeed, autonomous regulation has been associated with beneficial outcomes, for instance improved diabetes management and smoking cessation. However, in practice, health goals are often set for patients and not by patients, and often include behaviours that are not inherently enjoyable. Therefore, autonomy support from professionals could play an important role in successful self-regulation, for example by using the patient-centred techniques of motivational interviewing (e.g., to develop or identify autonomous reasons for behaviour change and set goals that fit patients’ personal life).

Self-efficacy beliefs are also a central aspect of self-regulation theory. Self-efficacy refers to peoples’ beliefs about their capabilities to perform a certain behaviour, and Bandura identified four factors affecting self-efficacy beliefs: performance accomplishments, vicarious experiences, verbal persuasion, and emotional arousal, with performance accomplishments (i.e., past experiences, that can raise [success] or lower [failure] self-efficacy) as the strongest factor. These self-efficacy beliefs are thought to influence the adoption and maintenance of goals and help people to persevere in spite of the barriers they face when striving to achieve their goals. Indeed, various studies demonstrate the importance of self-efficacy with respect to self-care behaviours, psychological outcomes and health outcomes in various patient populations including patients with ESKD. Furthermore, peoples’ sense of self-efficacy can also be modified, for instance by means of support strategies such as guided performance mastery, modelling, experience sharing, or stress management. Additionally, the strategy 'barrier identification and identify ways for overcoming them’ is often used to increase self-efficacy beliefs and facilitate behaviour change.

Another self-regulation cognitions that are considered important in goal selection and disease management are illness perceptions. Leventhal’s Common Sense Model of self-regulation proposes that when people are faced with symptoms, this will evoke cognitive and emotional perceptions, and these beliefs will help people to make sense of the situation they are confronted with (i.e., how serious and
controllable is the condition).\textsuperscript{88,89} These perceptions will also affect how patients respond to and cope with the illness, and subsequently contribute to health outcomes.\textsuperscript{109,110} Furthermore, this self-regulation framework posits that individuals appraise their initial coping efforts (i.e., did it bring me closer to the desired outcome), and the outcomes of these evaluations will feed back to the interpretation and action stages (i.e., following [un]successful disease management, illness perceptions may be changed and different coping responses may be planned and executed). This dynamic and cyclical process (see Figure 4) is thought to continue until people believe that the desired outcome is reached.\textsuperscript{89}

Over the years, the following interrelated illness perception domains have been identified: \textit{illness identity} (the number and type of bodily symptoms the individual attributes to the disease), \textit{causes} (the individual’s beliefs about the cause of the disease), \textit{timeline acute/chronic} (how long the individual expects the disease to last), \textit{timeline cyclical} (whether the individual believes that the disease and related symptoms have an unpredictable cyclical nature), \textit{consequences} (perceived impact of the disease on the individual’s life), \textit{personal control} (the degree to which the individual believes that the disease can be influenced by how they personally behave), \textit{treatment control} (the extent to which the individual believes that the disease can be effectively controlled by the treatment), \textit{illness coherence} (the individual’s perceived understanding of the disease), and \textit{emotional response} (the individual’s negative feelings about the disease).\textsuperscript{109,111}

Illness perceptions have been proven to relate to outcomes in different patient populations (e.g., patients with CVD, DM, cancer, and asthma),\textsuperscript{110} and there is also mounting evidence suggesting that illness perceptions play an important role in outcomes of patients with ESKD, including depressive symptoms,\textsuperscript{112,113} HRQOL,\textsuperscript{28,114–117} and mortality\textsuperscript{118,119} (see also Clark et al.,\textsuperscript{100} Parfeni et al.,\textsuperscript{120} and Chilcor\textsuperscript{121}). These findings match with the Common Sense Model of self-regulation, and may be partly mediated by inadequate coping behaviours and nonadherence to treatment.\textsuperscript{122–124} The relationship between illness perceptions and outcomes in patients prior to ESKD is investigated less often; the studies that have been conducted found illness perceptions to be associated with psychological well-being, symptom burden, coping strategies, perceived autonomy and self-esteem, however, all studies had a cross-sectional design and included a relatively small sample (i.e., 15 to 105 patients)\textsuperscript{125–129} (see also Clarke et al.\textsuperscript{130}).
Finally, meta-analyses and trials have also showed that multifaceted interventions based on self-regulation theory are effective in improving self-care behaviours, health outcomes, functional outcomes, and psychological well-being in different populations, including patients with CVD, DM, rheumatoid arthritis.\textsuperscript{106,131–136} There are a few studies that investigated the effectiveness of multicomponent self-regulation interventions in patients with CKD; these studies show that interventions comprising educational, cognitive and behavioural components (e.g., education, goal setting, self-monitoring, teaching stimulus control and coping skills, stimulating social support, monitoring and evaluating unhelpful beliefs, and relapse prevention) can improve self-efficacy in patient with CKD stages 1 to 3,\textsuperscript{137} (see also Welch et al.\textsuperscript{138}) and can improve adherence to fluid intake restrictions and psychological well-being in patients receiving dialysis treatment.\textsuperscript{139–141} Furthermore, Karamanidou and colleagues showed that a brief psycho-educational intervention based on self-regulation theory can result in improved understanding of phosphate-binding medication and medication outcome efficacy beliefs among patients receiving dialysis treatment.\textsuperscript{142}
Chapter 1

Aim

This dissertation aims to identify opportunities to slow down disease progression and improve HRQOL in patients with CKD prior to ESKD from a biopsychosocial, patient-centred and self-regulation perspective. These approaches will be applied throughout this dissertation by continuously investigating relationships between demographic, psychosocial and clinical factors and outcomes; exploring patients’ experiences, needs and preferences; examining the role of self-regulation cognitions in disease progression and HRQOL; investigating possibilities for individualized treatment; and evaluating patient-centred self-regulation strategies aimed to improve lifestyle behaviours.

Part one

The first part of this dissertation focuses on reducing sodium intake in patients with CKD stages 1 to 3. We aimed to identify which barriers patients face when they try to reduce sodium intake in their daily lives, assess how important these perceived sodium reduction barriers are, and investigate which subgroups of patients would benefit most from additional support strategies when striving to adhere to a low-sodium diet. We also aimed to explore patients’ needs and preferences regarding support strategies when striving to limit their sodium intake. Finally, we investigated whether a multi-component patient-centred self-regulation intervention could successfully support patients to reduce their sodium intake, and consequently improve clinical and psychosocial outcomes.

To this end, we conducted a qualitative study (i.e., focus groups with patient and health care professionals in four hospitals in the Netherlands), a cross-sectional study (i.e., a questionnaire survey combined with clinical data from medical records of one Dutch hospital), and a multicentre open randomised controlled trial (i.e., a study to evaluate the intervention’s effectiveness in four hospitals in the Netherlands).

Part two

The second part of this dissertation focuses on the identification of key factors associated with disease progression and HRQOL in patients receiving predialysis care. We aimed to explore if the combined association of Hb levels and anaemia medication with HRQOL differs in specific subgroups of patients, and to identify distinct
HRQOL trajectories during predialysis care. Additionally, we aimed to explore which factors (i.e., demographic and clinical factors, and illness perceptions) at the start of predialysis care are associated with specific HRQOL trajectories and disease progression during predialysis care.

To this end, we used already available data from a prospective observational study in the Netherlands, the PREdialysis PAient REcord-2 (PREPARE-2) study. In this study, data of 502 incident predialysis patients was collected from the moment they were referred to one of the 25 participating nephrology outpatient clinics, and every six months hereafter until the end of follow-up (i.e., transplantation, initiation of dialysis, recovered kidney function, death, or other study-related reasons for drop-out).

Outline of this dissertation

In the current Chapter of this dissertation (Chapter 1) information was provided about CKD, the consequences of CKD, and the regular care that patients receive in CKD stages 1 to 5. Additionally, we highlighted several gaps in renal scientific research and possibilities to improve nephrological care, after which we elaborated on the biopsychosocial, patient-centred and self-regulation perspective that form important sources of inspiration for the following six studies included in this dissertation.

Chapter 2: Perceived barriers and support strategies for reducing sodium intake in patients with chronic kidney disease: a qualitative study

To successfully support patients with CKD in reducing their sodium intake, in-depth knowledge about their experiences, needs and preferences is indispensable. However, to our knowledge, only one qualitative study reports on barriers and facilitators for sodium reduction in patients with CKD, and generalisation of these results is limited due to the specific group of patients included in this study (i.e., females of Bangladeshi origin living in the United Kingdom).143 Furthermore, three quantitative studies assessed the importance of sodium-reduction barriers by means of a questionnaire, but these studies were conducted in patients receiving dialysis treatment and the questionnaires included only a few sodium-barriers (3 or 5 barriers).144–146 Hence, these studies do not provide a comprehensive view of patients’ experience with a low-sodium diet prior to ESKD.
Therefore, we conducted focus groups with patients with CKD and health care professionals in order to identity perceived barriers and facilitators for reducing sodium intake. Literature suggests that patients and professionals may hold different views on self-management and on what is needed to successfully self-manage\cite{147} and thus, by including the perspective of professionals, we could identify similarities and differences. Finally, by using self-regulation theory as a framework, we gained insight into the behaviour change process of sodium reduction and also which type of support is needed in each phase of behaviour change.

Chapter 3: Perceived sodium reduction barriers among patients with chronic kidney disease: which barriers are important and which patients experience barriers?

The study described in Chapter 2 provides in-depth knowledge about patients’ experience with reducing sodium intake. However, this qualitative design is not suitable for the assessment of how common the identified sodium reduction barriers are in a broader population of patients with CKD and to examine which barriers are perceived as most important. Additionally, further research is warranted to examine which factors are associated with sodium reduction barriers, in order to identify patients that will most likely benefit from additional support. Previous studies show that demographic (e.g., gender, age, and level of education), medical (e.g., receiving treatment for a longer period of time and comorbidities), and psychosocial (e.g., self-efficacy, depressive symptoms, and perceived autonomy support) factors are associated with treatment adherence in patients with ESKD\cite{102,144,145,148-151} and hence, it is plausible that these factors are also related to difficulties with reducing sodium intake in earlier stages of CKD. Therefore, we conducted a cross-sectional study, using data from a questionnaire survey and medical records, to examine the importance of a broad range of sodium reduction barriers and investigate which factors are associated with these sodium reduction barriers.

Chapter 4: Sodium restriction in patient with chronic kidney disease: a randomised controlled trial of self-management support

Crossover trials show that if patients with CKD adhere to the sodium treatment guidelines, important risk factors for disease progression can be reduced\cite{40-42,51}. However, most patients with CKD do not reach the recommended sodium intake, and therefore, scholars stress the need for the implementation of behavioural support strategies\cite{50,51}.
Literature indicates that theory-based self-regulation interventions that encompass multiple behaviour change techniques are required to change lifestyle effectively, but such interventions to support patients with CKD to reduce their sodium intake are lacking. Therefore, we designed the ESMO (Effects of Self-Monitoring on Outcome of Chronic Kidney Disease) intervention; this three-month self-regulation intervention was tailored to the needs of patients and professionals, and consisted of education, motivational interviewing, coaching, and self-monitoring of blood pressure and sodium intake. A multicentre open randomised controlled trial was conducted to evaluate whether the intervention resulted in reduced sodium excretion, improved clinical outcomes (e.g., blood pressure, protein excretion, and kidney function) and improved psychosocial outcomes (i.e., HRQOL and self-efficacy) immediately after the intervention and at 6-month follow-up.

Chapter 5: Haemoglobin levels and health-related quality of life in young and elderly patients on specialized predialysis care

Using anaemia medication (ESA and/or iron supplement) to strive for high Hb levels (≥ 12 g/dL) can have positive outcomes (i.e., increased HRQOL), but could also increase the risks for adverse outcomes (e.g., a cardiovascular events) in patients with CKD. Therefore, the treatment guidelines state it is best to strive for a narrow Hb target (≥ 11 to ≤ 12 g/dL). This ‘one size fits all’ approach does not seem desirable and scholars stress the need for individualised anaemia treatment that takes into account patients’ preferences (e.g., for some patients an increased HRQOL is more important than an increased risk for a cardiovascular event). However, there is insufficient knowledge about the combined association of Hb levels and anaemia medication with HRQOL in order for professionals and patients to make well-considered treatment decisions. Furthermore, the CKD population is a highly heterogeneous group, and hence, identifying subgroups that respond differently to the anaemia treatment can be an important step towards individualised treatment approaches. One factor that should be taken into account is age; literature suggests that HRQOL differs depending on peoples’ age, and that age is important when determining Hb target levels using medication in patients with ESKD. Therefore, we used the PREPARE-2 data to examine the associations between different Hb levels and HRQOL during the first 2 years of predialysis care, and additionally, investigated if this association differed depending on age and the prescription of anaemia medication at the start of predialysis care.
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Chapter 6: Health-related quality of life trajectories during predialysis care and associated illness perceptions

Predialysis care aims to optimize HRQOL, however, it is unclear how HRQOL develops during predialysis care; some studies found decreased levels of HRQOL, others found no change in HRQOL, and there are studies that only found changes in one specific HRQOL domain. An explanation for these contradictory results could be that all studies examined mean levels of HRQOL over time, hereby masking individual variation in the course of HRQOL. So far, no studies have been conducted to examine distinct HRQOL trajectories during predialysis care and to investigate which factors are markers for unfavourable trajectories. Previous studies show that age, gender, body mass index, comorbidities, kidney function, and levels of albumin and Hb are associated with mean levels of HRQOL in patients with CKD, and thus, these factors may also be associated with HRQOL trajectories during predialysis care. Additionally, literature suggests that illness perceptions are associated with HRQOL in patients with ESKD, and thus, these self-regulation cognitions might also play a key role in HRQOL trajectories during predialysis care. Therefore, we used the PREPARE-2 dataset to investigate whether distinct HRQOL trajectories during the first 18 months of predialysis care could be detected, and to examine if these trajectories were associated with various demographic factors, clinical factors and illness perceptions. With this knowledge, patients with increased risk for unfavourable HRQOL trajectories can be identified and opportunities can be created for personalised treatment approaches to improve HRQOL.

Chapter 7: Illness perceptions in patients on predialysis care: associations with time until start of dialysis and decline of kidney function

Stronger negative perceptions of illness have been associated with various outcomes in patients with ESKD, including nonadherence to treatment and mortality. However, little is known about illness perceptions in earlier stages of CKD and no studies have been conducted that investigate the relationship between illness perceptions and accelerated disease progression in patients receiving predialysis care. It is important to address this gap in the literature because patients receiving predialysis care still have the opportunities to slow down kidney failure and delay the progression towards ESKD, for example by adhering to pharmacotherapy and lifestyle restrictions. By establishing
the relationship between illness perceptions and disease progression in patients receiving predialysis care, opportunities can be created to design support strategies aimed at slowing down the progression towards ESKD. Therefore, we used the PREPARE-2 data to investigate whether stronger negative perceptions of illness at the start of pre-dialysis care are a marker for an accelerated disease progression during predialysis care (i.e., an earlier start of dialysis and/or a faster decline of kidney function).

Finally, in Chapter 8 the main findings of this dissertation are described, followed by a discussion of our findings, the strengths and limitations of this dissertation, and suggestions for future research and practice will be provided.
Chapter 1

References


3. ERA-EDTA Registry. *ERA-EDTA registry annual report 2013.* Amsterdam, the Netherlands: Academic Medical Center, Department of Medical Informatics; 2015.


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