Disease progression and quality of life in patients with chronic kidney disease: the role of health behaviours and illness perceptions

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THE ROLE OF HEALTH BEHAVIOURS AND ILLNESS PERCEPTIONS

Yvette Meuleman

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Ziekteprogressie en kwaliteit van leven in mensen met chronische nierziekte: de rol van gezondheidsgedragingen en ziektepercepties

PROEFSCHRIFT
ter verkrijging van
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Door
Yvette Meuleman
geboren te 's-Gravenhage
in 1982

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Voor die ouwûh…

To heal does not necessarily imply to cure.
It can simply mean helping people to achieve a way of life compatible
with their individual aspirations – to restore their freedom to make choices –
even in the presence of continuing disease.

René Dubos, 1978

Contents

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 m^2 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]

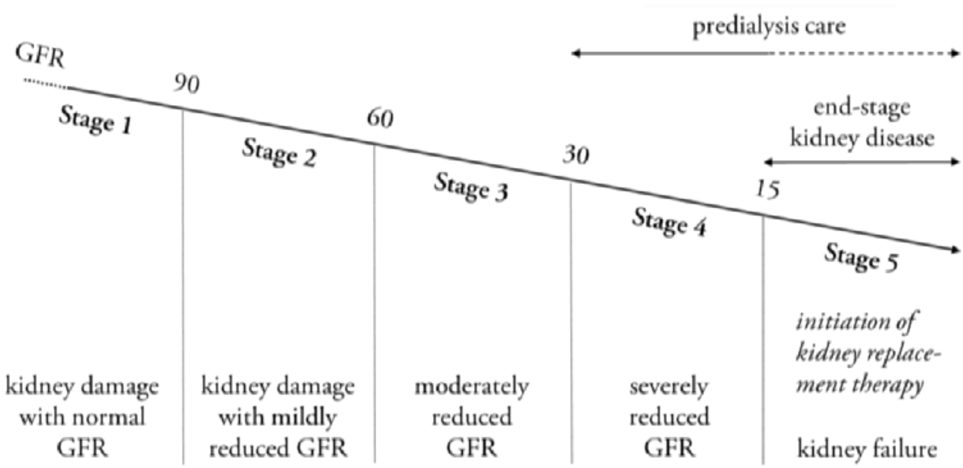

Figure 1. Classification of CKD stages

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.[3–6] Additionally, lifestyle factors such as smoking and obesity have been identified as risk factors for the development of CKD.[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%,[5,8] and the estimated prevalence of CKD in the Netherlands ranges between 6.7 and 12%.[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.[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.[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.[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^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.[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.[14–17]

Finally, as CKD progresses, the risk for mortality increases,[18] 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.[17,19,20] 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.[18,20,21]

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.[5] 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.[22,23] Additionally, patients with CKD that also received the diagnosis DM and CVD often experience more symptoms compared to patients without such comorbidities.[22]

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.[24] 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).[25] In patients with CKD, levels of HRQOL generally decrease as the disease progresses[26] and the most severely compromised levels of physical and mental HRQOL are found in patients receiving dialysis treatment.[27–29] 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).[26,30,31] 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.[22,23,32–35] Furthermore, lower levels of HRQOL in patients receiving predialysis care have been associated with a faster progression towards ESKD and mortality.[22,36]

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.[46,47] Moreover, a low-sodium diet reduces protein excretion,[40,41,48,49] increases the efficacy of RAAS-blockade medication,[50,51] and reduces the risk for cardiovascular complications and the progression towards ESKD.[52,53] 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.[37] 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).[51,54] 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.[50,51]

Treatment in CKD stages 4 and 5

When the kidney function drops below 30 mL/min/1.73 m^2, 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).[33,38]

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.[38,55] Often the preferred option is kidney transplantation because life expectancy and HRQOL is higher compared to other ESKD treatment options.[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.[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.[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,[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).[59] Consequently, the treatment guidelines advise to strive for a narrow Hb target (≥ 11 to < 12 g/dL).[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.

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".[60] In this paper, Engel state 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.[60,61]

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 biosychosocial model should be used as a framework for clinical practice, but also medical research and teaching.[60,61]

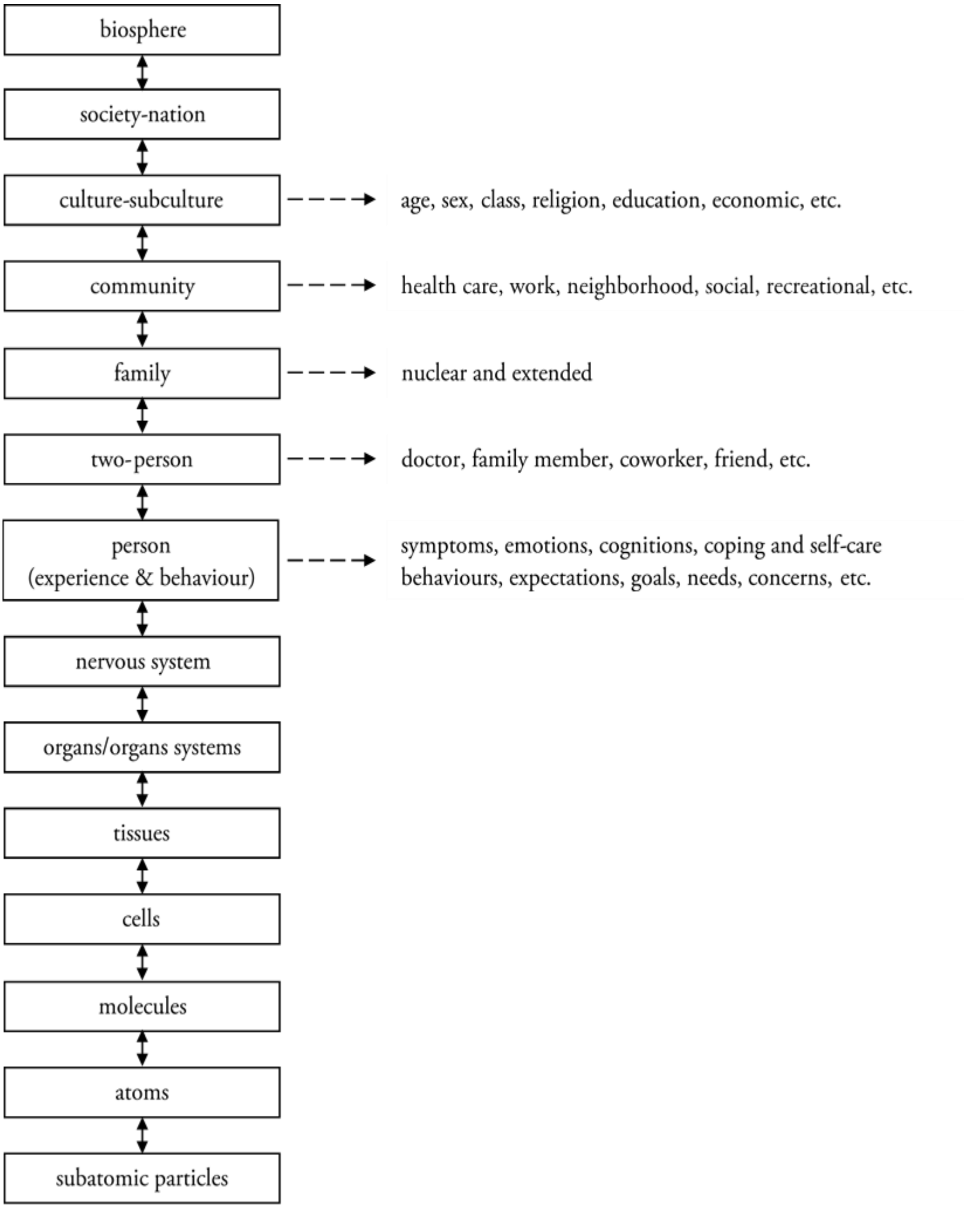

Figure 2. Visual presentation of the biopsychosocial model (adapted from Engel, 1981)[61]

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.[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.[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).[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.[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).[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.[68,69]

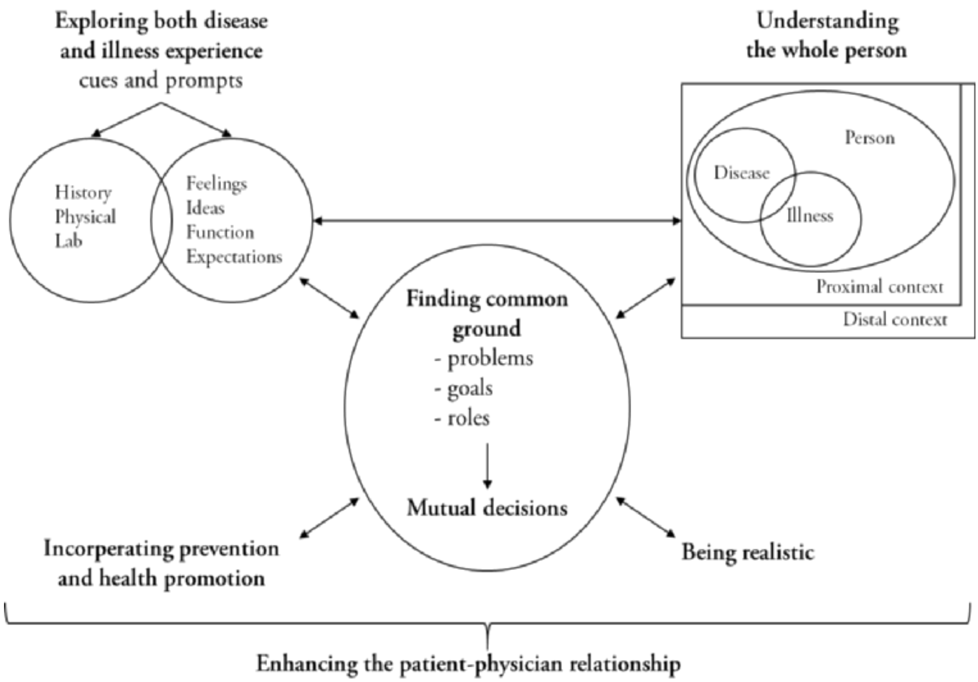

Figure 3. The patient-centred clinical method (adapted from Stewart and colleagues, 1995)[68]

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.[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.[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,[72–75] but evidence for such approaches in patients with CKD, especially prior to ESKD, is limited.[83]

Self-regulation perspective

Self-regulation theory is a psychological framework that is often used for understanding and explaining health and illness behaviours.[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).[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.[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.[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).[91] Indeed, autonomous regulation has been associated with beneficial outcomes, for instance improved diabetes management and smoking cessation.[92–96] 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).[97,98]

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.[84,99] 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.[100–103] 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.[104,105] Additionally, the strategy 'barrier identification and identify ways for overcoming them' is often used to increase self-efficacy beliefs and facilitate behaviour change.[106–108]

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).[88,89] These perceptions will also affect how patients respond to and cope with the illness, and subsequently contribute to health outcomes.[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.[89]

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

Illness perceptions have been proven to relate to outcomes in different patient populations (e.g., patients with CVD, DM, cancer, and asthma),[110] and there is also mounting evidence suggesting that illness perceptions play an important role in outcomes of patients with ESKD, including depressive symptoms,[112,113] HRQOL,[28,114–117], and mortality[118,119] (see also Clark et al.,[100] Parfeni et al.,[120] and Chilcot[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.[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)[125–129] (see also Clarke et al.[130]).

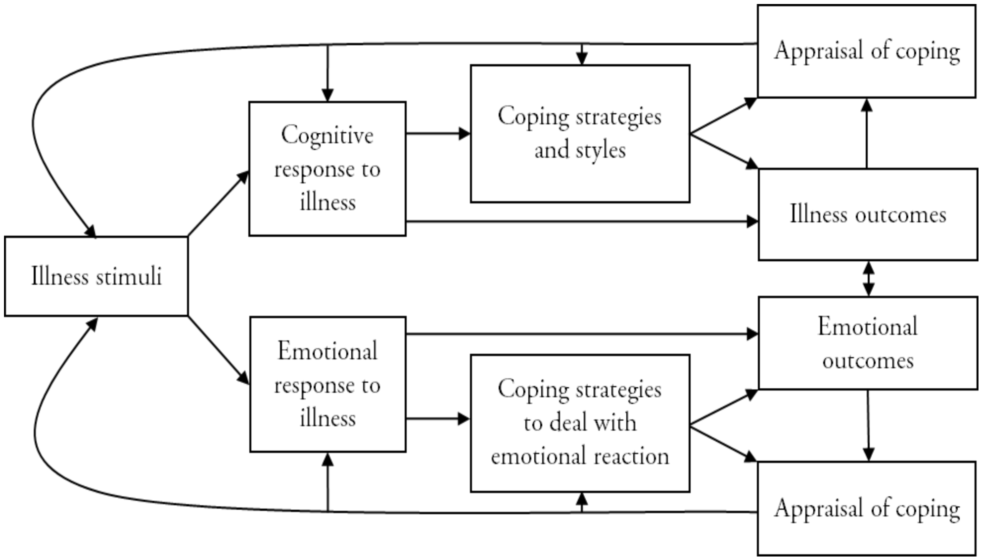

Figure 4. Visual representation of Leventhal's Common Sense Model of self-regulation (adapted from Hagger & Orbell, 2003)[110]

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.[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,[137] (see also Welch et al.[138]) and can improve adherence to fluid intake restrictions and psychological well-being in patients receiving dialysis treatment.[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.[142]

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 PAtient 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 patient 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 biopsycho-social, 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,[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,[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.[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.[50,51]

Literature indicates that theory-based self-regulation interventions that encompass multiple behaviour change techniques are required to change lifestyle effectively,[85,106,131,132] 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),[58] but could also increase the risks for adverse outcomes (e.g., a cardiovascular events) in patients with CKD.[59] Therefore, the treatment guidelines state it is best to strive for a narrow Hb target (≥ 11 to ≤ 12 g/dL).[33,38] 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).[152,153] 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,[29] and that age is important when determining Hb target levels using medication in patients with ESKD.[154] 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.

Chapter 6: Health-related quality of life trajectories during predialysis care and associated illness perceptions

Predialysis care aims to optimize HRQOL,[33,38] however, it is unclear how HRQOL develops during predialysis care; some studies found decreased levels of HRQOL,[22,155,156] others found no change in HRQOL,[157,158] and there are studies that only found changes in one specific HRQOL domain.[159–161] 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,[26,30,155,157,160,162] 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,[28,114–117] 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.[118,119,122,123] 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.[1,14,15,38] 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.

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Chapter 2

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

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Abstract

Background

Reducing sodium intake can prevent cardiovascular complications and further decline of kidney function in patients with chronic kidney disease. However, the vast majority of patients fail to reach an adequate sodium intake, and little is known about why they do not succeed.

Purpose

This study aims to identify perceived barriers and support strategies for reducing sodium intake among both patients with chronic kidney disease and health care professionals.

Methods

A purposive sample of 25 patients and 23 health care professionals from 4 Dutch medical centres attended 8 focus groups. Transcripts were analysed thematically and afterwards organized according to the phases of behaviour change of self-regulation theory.

Results

Multiple themes emerged across different phases of behaviour change, including the patients' lack of practical knowledge and intrinsic motivation, the maladaptive illness perceptions and refusal skills, the lack of social support and feedback regarding disease progression and sodium intake, and the availability of low-sodium foods.

Conclusions

The results indicate the need for the implementation of support strategies that target specific needs of patients across the whole process of changing and maintaining a low-sodium diet. Special attention should be paid to supporting patients to set sodium-related goals, strengthening intrinsic motivation, providing comprehensive and practical information (e.g., about hidden salt in products), increasing social support, stimulating the self-monitoring of sodium intake and disease progression, and building a supportive patient-professsional relationship that encompasses shared decision making and coaching. Moreover, global programs should be implemented to reduce sodium levels in processed foods, introduce sodium-related product labels, and increase consumer awareness.

Introduction

The prevalence and incidence of chronic kidney disease (CKD) is rising worldwide and can be attributed to an aging population[1] and to the global increase of weight excess and of type 2 diabetes mellitus.[2] With the progression of CKD, the burden of the disease for individual patients and health care costs increases.[3] Therefore, better prevention in earlier stages of CKD is urgently needed.

An important treatment strategy to prevent further decline of kidney function is reducing dietary sodium intake. Firstly, because hypertension is a common feature of CKD and striving for adequate blood pressure regulation not only decreases risk of cardiovascular complications,[4,5] but retards progression of kidney failure as well.[6,7] Secondly, sodium restriction reduces urinary loss of protein,[8] which is directly involved in the pathogenesis of tubuleinterstitial fibrosis of the kidney[9] and thereby loss of kidney function.[10,11]

Unfortunately, changing lifestyle is difficult to achieve.[12] In the Netherlands, research has shown that the average salt intake of patients with CKD is equal to the excessive salt intake of the general population of 9 - 12 g/day.[13,14] Indeed, 83% of the patients with CKD do not reach the recommended salt intake of 5 - 6 g/day.[15,16] It appears that current health care does not provide sufficient support for patients with CKD to incorporate the sodium treatment recommendation into their daily life and therefore implementing additional support strategies into health care is vital. However, to develop effective support strategies, in-depth knowledge about patients' needs and preferences is indispensable.[17] To our knowledge, few studies have focused on the perceived barriers and facilitators of patients with CKD for reducing sodium intake, and none of these studies included the perspective of health care professionals.[18,19] By also including professionals, similarities and differences between patients and professionals can be discussed and incorporated in the design of support strategies. Furthermore, none of the studies relied on a theoretical framework such as self-regulation theory: a frequently used theoretical perspective of understanding self-care behaviour that can provide us with practical guidelines for interventions aimed at behaviour change.[20,21,22] The self-regulation theory regards successful behavioural change as a "process" in which three "phases of behaviour change" should be considered: a motivational phase (in which patients develop the intention to change health behaviour), an action phase (in which patients actively try to change health behaviour), and a maintenance phase (in which patients succeed or fail to maintain new health behaviour).

In the current study, we conducted focus groups with patients and professionals to identify perceived barriers and support strategies for reducing sodium intake and to organize these barriers and support strategies according to the phases of self-regulation theory afterwards. By using self-regulation theory as a framework, insight is gained into the behaviour change process of reducing sodium intake among patient with CKD and which type of support is needed in each phase of behaviour change.

Methods

Design and participants

This qualitative study is part of the Effects of Self-Monitoring on Outcomes of Chronic Kidney Disease (ESMO) study in which a self-management intervention is designed and evaluated. Eight focus groups were conducted between June and November 2010 until data saturation (i.e., until no new themes emerged and information was obtained)[23] was reached with a purposive sample of 25 patients and 23 health care professionals from 4 Dutch medical centres. In each centre, two focus groups were conducted, one with patients and one with professionals. We invited patients in varying CKD stages, who had positive as well as negative experiences with reducing sodium intake. Patients on dialysis were excluded to limit heterogeneity in treatment characteristics (e.g., prevent further decline in kidney function is not an option anymore and dialysis is needed to sustain life). In addition, different professionals involved in the CKD treatment were invited (i.e., nephrologists, nurse practitioners, dieticians, and social workers) to make sure various occupational perspectives were included. All participants received information regarding the procedure of the study, emphasizing the confidentiality and anonymity. The study was approved by the medical ethics committee of all participating medical centres, and written informed consent was obtained from all participants.

Interview and data collection

Based on literature and a pilot focus group with members of the Dutch Association of Kidney Patients, an interview protocol was developed to maintain consistency in the format of the focus groups. In Table 1, the protocol of the focus groups is shown. The focus groups lasted about 2 hours, were carried out by the investigator (Y.M.), and recorded digitally. Two observers (L.t.B. and S.v.D.) recorded field notes on group dynamics and nonverbal communication. Prior to the interview, participants completed a brief questionnaire to collect sociodemographic information. During the interview, participants were asked about their experiences with reducing sodium intake and about the adequacy of current health care support. All questions were open-ended and responses were further explored by using additional questions and probes. At the closing of the interview, all participants completed a questionnaire concerning the need for additional support in reducing sodium intake: participants rated the importance of multiple support strategies on a 10-point scale ranging from 1 'not important' to 10 'very important'. In addition, they were encouraged to write down all their personal ideas and comments.

Table 1. Interview protocol of the focus groups [a]

1. Can you tell us something about yourself?
2. Did you receive an advice to reduce your sodium intake?
3. Can you tell us something about your experiences with reducing your sodium intake?
4. What makes/made it difficult for you to reduce your sodium intake? Why?
5. What helps/has helped you to reduce your sodium intake? Why?
6. What kind of support do/did you receive?
7. What kind of support do/did you need, but was not provided?
8. What is the best way to support patients in reducing their sodium intake?
9. If you have the opportunity to design your own program to support patients with CKD, which strategy should be included in a program to reduce sodium intake? And how important (on a scale from 1 to 10) would you rate each strategy in the program?
   - Blank spaces for personal ideas
   - Fixed component and blank spaces for additional comments:
     - Self-monitoring sodium
     - Self-monitoring blood pressure
     - Keep a nutrition diary
     - Feedback
     - Information about.............
     - Individual meeting about.............
     - Group meeting about.............

[a] In questions four to seven of the the interview protocol with professionals "you" was replaced by "patients with CKD".

Analysis

All sessions were transcribed in full and reviewed line-by-line by the investigator (Y.M.). The transcripts were first analysed thematically[24] by Y.M., and a coding scheme was created by constant comparison, grouping similar themes and organizing them hierarchically. Two authors (S.v.D. and L.t.B.) also coded transcripts, to judge consistency of interpretation. The themes were compared and discussed. The analysis was conducted deductively afterwards: identified themes from the inductive analysis were now organized according to the three phases of behaviour change of self-regulation theory.

Results

Sample characteristics

Each focus group involved four to nine participants. The focus groups with patients consisted of 15 males and 10 females with a mean (standard deviation [SD]) age of 60.6 (11.7) years. The health care professionals participating in the focus groups were involved in the treatment of patients with CKD for a median (boundaries of interquartile range [IQR]) duration of 6.0 (14.0) years. The characteristics of all participants are shown in Table 2.

Themes

Eight main themes were identified and afterwards organized across three phases of behaviour change.

Motivational phase

1. Knowledge. Most patients reported that they received insufficient information from professionals, in particular about practical issues, and wanted to discuss the personal implications of the information given:

> I need more information…and to discuss it into more detail. Not just the remark: 'Everything goes well, but your kidney function is declining'. Yes, OK…but how much? And what can I do about it! (Patient, male, age 66)

Many patients searched for additional information on the Internet, but some patients stumbled upon scary and unreliable information. Conversely, most professionals reported that they provided patients with a lot of information, although patients still seemed to lack knowledge:

> Sometimes it is stunning that, even though patients pay regular visits for many years, they still do not have the slightest notion of what a kidney does. (Nurse practitioner)

Table 2. Participant characteristics of patients with CKD (N = 25) and professionals (N = 23) [a]

	Patients	Professionals
Participants medical centre, n (%)		
Leiden University Medical Centre	5 (20.0)	6 (26.1)
Academic Medical Centre Amsterdam	7 (28.0)	6 (26.1)
University Medical Centre Groningen	9 (36.0)	5 (21.7)
Sint Antonius Hospital Nieuwegein	4 (16.0)	6 (26.1)
Sex, male, n (%)	15 (60.0)	7 (30.4)
Age, years, mean ± SD	60.6 ± 11.7	43.0 ± 11.8
Marital status, n (%)		
Married/Partnered	18 (72.0)	20 (87.0)
Single	7 (28.0)	3 (13.0)
Having children, yes, n (%)	20 (80.0)	13 (56.6)
Ethnicity, Dutch, n (%)	22 (88.0)	22 (95.7)
Religious, yes, n (%)	11 (44.0)	6 (26.1)
Highest level of education, n (%)		
Primary education	2 (8.0)	
Secondary education	7 (28.0)	
Vocational education	7 (28.0)	
Tertiary education (college/university)	9 (36.0)	23 (100)
Work status, n (%)		
Full-time	6 (24.0)	14 (60.9)
Part-time	5 (20.0)	9 (39.1)
No - Home/retired	7 (28.0)	
No - Disabled due to health	7 (28.0)	
Kidney transplantation, n (%)	5 (20.0)	
Health care profession, n (%)		
Nephrologist/internist		10 (43.5)
Nurse practitioner		1 (4.3)
Dietician		7 (30.4)
Nurse		2 (8.7)
Social worker		2 (8.7)
Physician assistant		1 (4.3)
Involved in CKD treatment, years, median (IQR)		6.0 (14.0)

[a] Continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables, and skewed variables as median and boundaries of interquartile range (IQR).

Professionals suggested that information tailored to the individual patient (e.g., according to age, culture or level of intelligence) could be helpful to increase patients' uptake of information. Some professionals were also concerned about patients' lack of illness insight, for example patients who believe they have no control over their disease. Although professionals felt that repeatedly emphasizing the importance of lifestyle would be beneficial, they reported a lack of time to address patients' illness insight adequately.

2. Motivation. Most professionals believed that many patients lack a strong intrinsic motivation to reduce their sodium intake. In contrast, patients did not mention strong personal reasons about why they should reduce their sodium intake but talked about having to reduce their sodium intake because their nephrologist told them so. However, patients brought forward strong personal reasons about why they did not want to reduce their sodium intake:

> I eat everything. See if I care! Even before my transplant, 2 years ago, I ate everything. With a diet for my diabetes and my kidney disease, I cannot eat anything. Yes, 42 pills a day, but what else? It is all rubbish! (Patient, male, age 68)

The majority of patients and professionals stated that often patients are reluctant to reduce their sodium intake because of the unpleasant taste of sodium-free food and the great burden of having to adhere to multiple lifestyle restrictions. According to most professionals, motivation to change behaviour only gets sufficiently strong if the threat of ongoing disease gets serious enough:

> Usually, patients become more motivated when you make a detour with them across the dialysis ward. Then they start asking questions like: 'What can I do to postpone dialysis as long as possible?' It's threatening to be confronted with what is ahead of them. (Nephrologist)

Many professionals and some patients reported that the lack of motivation could be explained by the lack of physical symptoms:

> Apparently, I am a kidney patient, but I do not notice it. I disregard everything: I eat everything, I drink everything, and I smoke everything. I would rather die than let myself be restricted too much. Look, when you are terminally ill, that's a different story. But as long as you are not… (Patient, male, age 75)

According to many professionals, patients would be motivated when convinced that changing lifestyle can postpone dialysis, decrease the amount of medication, and increase the opportunity for transplantation. Therefore, professionals believed that strengthening intrinsic motivation should be a key element of treatment. However, some professionals stated that in reality, professionals often motivate patients extrinsically by just telling them what to do.

3. Goal setting. Many professionals stressed the importance of setting realistic and concrete goals for reducing sodium intake, and some added the need for attainable steps to guide these goals:

> Lifestyle should be connected to treatment by setting personal goals and letting patients decide which little steps they take to attain those goals. (Nurse practitioner)

However, patients did not mention goal setting or planning but rather talked about what the professional told them to do:

> The nephrologist referred me to a dietician because I ate too much sodium. She told me I had to start a sodium-free diet and this was really hard for me to hear. I tried to cook without sodium, but the next consult she told me this was not enough. I had to give up olives as well… (Patient, female, age 52)

Action phase

4. Coping. The majority of patients and professionals agreed that coping with a sodium restriction is difficult. Many patients and professionals reported that handling eating outdoors and refusing food that is offered on parties is especially difficult:

> Most of the time they do well at home. But when they eat out, they think: 'How am I going to manage this?' and if you don't have the skills to refuse…you just find yourself eating it. (Social worker)

Some patients even avoid social gatherings completely to refrain from salty foods:

> Yes, eating sodium is a problem. You cannot participate in anything or go anywhere. (Patients, male, age 52)

To be able to persevere, many patients reward themselves frequently (e.g., with a salty snack) and a few patients reported that, despite the burden of CKD, they tried to cope positively and focus on the things they can still do. Many patients indicated that they benefited greatly from a referral to a dietician, because they provided them with practical information (e.g., reading product labels, cookery books or the use of herbs). However, some patients and professionals stressed the importance of referral to a dietician in an earlier stage of CKD. Many professionals believed that the key element in better coping with the restriction lies in patients themselves, namely to take up a more active role.

5. Feedback. Most patients and professionals believed that patients could benefit greatly from regular self-monitoring of dietary intake (e.g., sodium intake due to hidden salt in food) and disease progression (e.g., blood pressure or creatinine levels). Many patients reported that self-monitoring tools would give them frequent and direct feedback and consequently make them more actively involved in the treatment:

> I am eager to measure, for instance, my sodium intake at home regularly. I want to be serious about my disease; steer my own treatment and contribute as much as possible to postpone dialysis. (Patient, female, age 60)

The majority of professionals stated that self-monitoring is needed to improve patients' empowerment and would make this asymptomatic disease more "real" to patients:

> If patients measure at home, they get direct feedback which makes the disease more real to them. It's important to show patients the effect of their sodium reduction. To make them realize they can also make a difference themselves and not just depend on medicine. (Nephrologist)

Additional self-monitoring possibilities are welcomed by most patients and professionals, provided that patients receive sufficient instructions and support from professionals. However, a few patients explicitly stated they did not want to engage in self-monitoring, because it is stressful and it is not desirable to "play doctor" themselves:

> Being a physician is a profession, just like driving a bus. And as long as the bus does not end up in the ditch… than I have all the confidence in the driver. I just want a physician who tells me what I should do. Because there is nothing I can do myself! (Patient, male, age 78)

Most professionals also emphasized that self-monitoring is not suited for nor wanted by all patients.

6. Support. The majority of patients indicated missing talking to fellow patients regarding practical issues but did not want to exchange "sad problem stories" (i.e., complain about everything). They also felt that professionals should involve patients' partners more actively in the treatment:

> I wish I had received better support from health care professionals. Also for my partner, because my partner does the cooking. When I come home from the dietician, I give the information to her. Then she says: 'What do I have to do with this?'. That is difficult, especially because I have already forgotten half of the stuff that has been said. (Patient, male, age 69)

Many patients and professionals believed that "patient-centred" care was needed to adequately support patients but felt that this was sometimes missing. Often, a treatment advice is given, without discussing the individual patients' needs and preferences. Many professionals pointed out that honesty, positive stimulation, evaluation, and complimenting patients on progression are essential:

> It's a hard and long road; often you have small successes in the beginning, but it has to be continued. As a professional you have to be on top of it, keep stimulating and patting them on the back. (Nephrologist)

However, professionals often felt a lack of time to adequately support patients.

Maintenance phase

7. Adaptation. The majority of patients adopted a more creative way of cooking, which is an important step in maintaining a low-sodium diet according to many professionals:

> Kidney patients cannot have ready-to-eat meals. They have to make everything themselves and this is difficult because often they feel tired. We need to support patients and teach them how to prepare sodium-free meals. (Dietician)

In addition, some patients now cooked separately for other members of the family. Some patients also bought low-sodium products regularly, and a few professionals added that it is unfortunate that these products are expensive. The majority of patients and professionals agreed that eating less sodium remains very time and energy consuming, because almost all products contain sodium:

> It's hard because you have to go through the supermarket thinking repeatedly 'What should I eat? Or actually 'What can't I eat'. There are so many things you just cannot have any more. (Patient, female, age 28)

Some professionals also added that, in order to succeed in maintaining a low-sodium diet, society has to change as well:

> It is not just the patient who should reduce his sodium, everybody should do it: restaurants, supermarkets and so on. If you want to reduce your sodium intake to the norm of 5 - 6 grams of salt a day, the food industry must cooperate, and otherwise it is not feasible. (Dietician)

8. New habit. The majority of patients seriously tried to reduce their sodium intake but reported that following a low-sodium diet was still difficult and not a new habit yet:

> I am not really used to eating less sodium yet… I have to keep repeating to myself 'You cannot have this'. I try to pay attention to it, but it's still hard… (Patient, female, age 42)

A few patients reported they had no problems with reducing their sodium intake and others had decided that they would not change their sodium intake at all. All professionals believed that despite attempts to reduce sodium intake, most patients only partially adhere to the restriction or do not succeed in maintaining a low-sodium diet in the long-term:

> Some people do extremely well in reducing their sodium intake, but the majority does not succeed. The average sodium intake is very high. Often there are small improvements in the beginning, but usually they are too small to improve health in an important way. (Nephrologist)

Support strategies

All participants rated the importance of strategies to support patients in reducing sodium intake on a 10-point scale. The three most important components rated by patients were as follows: self-monitoring sodium (mean [standard deviation {SD}] was 7.4 [2.2]), information (mean [SD] was 7.4 [1.6]), and feedback (mean [SD] was 7.2 [1.6]). Professionals rated feedback (mean [SD] was 8.4 [1.2]), individual meeting (mean [SD] was 8.0 [1.1]), and self-monitoring blood pressure (mean [SD] was 8.0 [1.1]) as most important. In Table 3, the list with strategies including additional comments is shown.

Table 3. Strategies to support patients in reducing sodium intake by patients with CKD (N = 25) and health care professionals (N = 23) [a]

Support strategies	Rated importance (mean ± SD) [b]	Additional comments
Self-monitoring sodium	P: 7.4 ± 2.2 H: 7.6 ± 1.4	- A really simple device is necessary (P&H) - Desirable if enough information and feedback is available (P) - Beware of obsessive measuring and panic (P) - Only if it doesn't takes too much time and energy (H) - Provides insight and direct feedback (P&H) - To verify progression of reducing salt intake (P&H)
Self-monitoring blood pressure	P: 6.9 ± 2.1 H: 8.0 ± 1.1	- Already used by patients often (P) - Beware of obsessive measuring and panic (P&H) - Good to avoid the white coat effect (H) - In combination with measuring nutrition (H)
Keeping a nutrition diary	P: 5.9 ± 1.6 H: 7.2 ± 1.3	- Too much work to fill it in (P&H) - Only effective when starting sodium reduction (P&H) - Stimulates awareness (H) - Not effective for everybody (H) - Use it as control measure for self-monitoring sodium (H)
Feedback	P: 7.2 ± 1.6 H: 8.4 ± 1.2	- Not only negative, but also positive feedback (P) - More feedback through telephone and computer (P&H) - More direct feedback is needed (P&H) - Guide patients to attain goals and make adjustments (H)
Information	P: 7.4 ± 1.6 H: 7.9 ± 1.5	- About nutrition, medication, complications, stress, health and lifestyle (P&H) - Information tailored to patient characteristics (H) - Oral as well as written education (H)
Individual meeting	P: 6.5 ± 1.9 H: 8.0 ± 1.1	- Topics: nutrition, medication, risk factors and coping (P&H) - Talking about problems including work related problems (P&H) - To increase intrinsic motivation (H) - To acquire skills to maintain healthy lifestyle (H) - Continuous evaluation with patient (H)
Group meeting	P: 6.4 ± 1.9 H: 7.0 ± 1.3	- Topics: nutrition, lifestyle, exercise, potassium (P&H) - Share experiences and advices (P&H) - Contact with fellow patients (H)
Personal ideas	- Smoking cessation (P) - Physiotherapy (H) - Multidisciplinary teams, in close cooperation with general practitioners (H) - Creative cooking course (P&H) - Advices regarding coping with multiple diseases (P) - Using medication passport (P) - A continuous coaching process (H) - Government support of sodium reduction in all food products (H) - Public health campaign (H) - Reliable information on Internet (P&H) - Clear food labels on products (H) - Motivational interviewing (H) - Psychosocial support (H)	

[a] P = Patients with CKD & H = Health care professionals. [b] Rated importance is presented as mean ± standard deviation (SD).

Discussion

This study identified multiple barriers of patients with CKD for reducing sodium intake and hereby provides us with explanations why the majority of patients do not succeed in reducing their dietary sodium intake. Furthermore, various support strategies tailored to the needs and preferences of patients with CKD and health care professionals can be derived from this study. Importantly, patients and professionals identified many different barriers, and these barriers correspond with different phases of behaviour change. The results indicate that support for patients in reducing sodium intake should not be limited to a single strategy at a fixed moment during treatment. This need for a multifaceted approach is in line with previous research that suggests that multicomponent interventions are most effective, especially for long-term adherence.[22,25] Moreover, a wide array of strategies was rated as being important for adequately supporting patients, including the need for additional feedback, information, different self-monitoring possibilities, and meetings (e.g., about coping with the disease and lifestyle). This suggests that, in accordance with the literature,[26-28] patients with CKD could benefit from additional support strategies that enhance self-management. The perceived barriers and various strategies to support patients with CKD will be discussed below using self-regulation theory as a theoretical framework.

In the *motivational phase*, there seems to be an important discrepancy between the amount of information given as reported by professionals and patients' perceived lack of information. The lack of knowledge in patients with CKD has been identified in previous research,[29] and this current study suggests several strategies to solve this discrepancy and increase patients' knowledge. Firstly, it is important that professionals not only provide patients with written information about the disease and the treatment. These patient education materials are often too complex, and it would be helpful if education materials would contain simple text and complementary pictures.[30] Furthermore, professionals and patients should discuss whether patients understand the information that is given, especially in specific subgroups like older patients or patients with limited health literacy.[29] More importantly, this factual information about the disease or treatment does not always seem to fit patients' needs. Patients indicate they need more practical information about how to cope with the disease and lifestyle restrictions. Secondly, solely providing patients with standard information and repeatedly emphasizing the importance of a healthy lifestyle are insufficient. Professionals should engage in a conversation with patients and prevent one-way communication: professionals could for example start by asking patients what they already know and/or want to know about the disease or treatment. This will not only improve the patient-professional interaction but will also increase adherence and the uptake of information.[31] In a similar vein, professionals can discuss how patients interpret and emotionally respond to the information, as professionals were concerned about patients' lack of illness insight. For example, patients who do not believe that kidney disease can be influenced by their personal behaviour (e.g., lifestyle) will probably not initiate a sodium reduction. A practical tool for identifying dysfunctional illness beliefs is the Brief Illness Perception Questionnaire.[32] Identifying and openly discussing illness perceptions is important, as illness beliefs are associated with adherence[33-35] and even mortality.[36,37] Furthermore, professionals indicated that patients sometimes seem to be lacking intrinsic motivation and patients did not mention intrinsic reasons to reduce their sodium intake: it seemed as if they primarily wanted to reduce their sodium intake because their nephrologist told them so. This poses a problem, because extrinsic motivation hampers the maintenance of a low-sodium diet, especially when patients feel overwhelmed by the multiple lifestyle restrictions, dislike the taste of sodium-free food,[18,19] and do not yet perceive their ongoing disease as a threat because they do not yet experience physical symptoms as a cue to action. The difficulty of encouraging asymptomatic patients to adhere to medical advice has been pointed out previously in patients with CKD[38] and hypertensive patients.[39] An effective strategy to enhance patients' intrinsic motivation is to train professionals in the patient-centred techniques of motivational interviewing.[40] By incorporating motivational interviewing skills into the consult, professionals will be less inclined to impose their opinion about why patients *should* be motivated to change their lifestyle but instead provide the opportunity to discuss personal reasons about *why* it may be important for that particular patient to change his or her health behaviours, including dietary adherence.[41,42] Furthermore, our results indicate that, even though professionals considered setting goals as important, patients did not talk about personal goals, and this could suggest that shared decision making is not a common element of health care yet.[43] Again motivational interviewing can contribute, as setting concrete and personal goals in close collaboration between patients and professionals is a key element.[40]

In the *action phase*, there are various strategies to support patients in coping with the sodium restriction on a daily basis. Firstly, referral to a dietician in an earlier CKD stage is recommended in order to provide patients with sufficient instructions and practical information (e.g., hidden salt in foods, cookery books, or the use of herbs). The latter is important, because understanding a medical advice does not automatically imply that patients are capable of incorporating recommendations into their daily life.[27] Furthermore, dieticians can help patients to comprehend the complicated food labels, but it would be more effective if foods would be fitted with a front-of-pack label, for example a label indicating "low or reduced in salt" or traffic light labels indicating high or low levels of salt. Studies have shown that this could be helpful in reducing sodium intake[44] and could positively influence purchase intentions in the general population.[45] Secondly, providing patients with additional self-monitoring tools could help them manage their disease, stimulate their autonomy, and would give them more frequent and direct feedback. Self-monitoring has already been identified as useful in other patient populations,[46-48] but is possibly even more beneficial in patients with CKD due to the asymptomatic nature of the disease and hidden salt in food. It should be noted that self-monitoring is not suited for nor wanted by all patients, and it is essential that patients who are willing to engage in self-monitoring receive sufficient training prior to self-monitoring and feedback and support from professionals. A third strategy could be that social workers teach patients refusal skills, as patients found it difficult to resist temptations.[18] Teaching assertive but socially appropriate refusal skills is likely to increase adherence and could empower patients to feel capable of refusing food instead of withdrawing from social events. Moreover, advertising and social marketing campaigns are needed to raise the general consumer awareness regarding sodium,[44] since the majority of consumers underestimate their own salt intake and lack of knowledge regarding the main sources of salt intake in their diet and are unaware of the salt recommendations.[49] Perhaps, by increasing consumer awareness, people within the social environment of patients would also pay more attention to their sodium intake and, consequently, create fewer situations where patients need to refuse foods. This is especially important, because the impression is that some patients feel alone in dealing with restrictions. Patients need to receive sufficient social support from their social environment, as literature has shown that social support is associated with adherence to medical treatment[35,50] and chronic illness self-management, especially regarding dietary behaviour.[51] The fourth and fifth strategy also concern additional social support: professionals can contribute by actively involving partners of patients in the treatment, and patient associations can contribute by creating easily accessible opportunities to meet fellow patients and share practical advices, for instance cooking workshops or Internet panels.

In the *maintenance phase*, it seems that most patients have seriously tried to reduce their sodium intake but found it difficult to maintain a low-sodium diet. For most patients, it was not a new habit yet. There are several possible strategies to support patients in maintaining a low-sodium diet and adhere to it in a strict way. Firstly, professionals should continue to stimulate patients to cook creatively and experiment with alternative sodium-free products. Secondly, the coaching role of all professionals is especially important in this phase: this role implies continuously evaluating and addressing problems that occur.[52] Moreover, patients should be complimented on progression and stimulated to keep trying to reduce their sodium intake, even though it is time- and energy-consuming. Finally, as 75% of the daily sodium intake comes from processed foods,[53] it is crucial that the sodium content of processed foods is reduced and better access to affordable low-sodium foods is provided. Initiatives for reducing the high sodium content in processed and catered foods have been taken and demonstrated promising results, but there is still a lot of room for improvement.[44,54]

The strength of this qualitative study is that it provides in-depth knowledge about daily experiences with reducing sodium intake of both patients with CKD and professionals. By identifying perceived barriers, the study offers answers to the underresearched question of why the vast majority of patients do not succeed in reducing their dietary sodium intake. Moreover, by identifying perceived support strategies, effective strategies tailored to the needs and preferences of patients and professionals can be developed and implemented into health care.

A limitation of this study is the research reflectivity. Although multiple investigators have judged the results, we cannot rule out the possibility that theoretical preconceptions have coloured the interpretation of data, for example by using a somewhat more cognitive and individual-focused theory like the self-regulation theory in the deductive part of the analysis, instead of a more socially oriented theory. Furthermore, additional research is needed to investigate whether these results can be generalized to different populations and different health behaviours. Moreover, this indepth knowledge should be quantified to gain insight into the association between the identified themes and factors like sociodemographic characteristics (e.g., age or living situation), psychosocial factors (e.g., depression), or clinical characteristics (e.g., kidney function, blood pressure, or sodium intake). Finally, a randomised controlled trial is needed to further investigate whether the suggested support strategies indeed improve health outcomes in patients with CKD.

Conclusions

When reducing sodium intake, patients with CKD experience multiple barriers in different phases of their behaviour change. Therefore, additional support strategies should be implemented into health care to prevent cardiovascular complications and further decline of kidney function. To adequately support patients with CKD in reducing their sodium intake, strategies should target specific needs of patients across the whole process of changing and maintaining a low-sodium diet. Special attention should be paid to strengthening intrinsic motivation, increasing self-monitoring possibilities and social support, providing practical information, and building a supportive patient-provider relationship that encompasses shared decision making and coaching. Moreover, to successfully maintain a low-sodium diet, global programs should be implemented to reduce the sodium levels in processed foods, introduce sodium-related product labels and increase consumer awareness.

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Chapter 3

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

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Abstract

Purpose

The purposes of this study were to assess the importance of perceived sodium reduction barriers among patients with chronic kidney disease (CKD) and identify associated sociodemographic, clinical, and psychosocial factors.

Methods

A total of 156 patients with CKD completed a questionnaire assessing sodium reduction barriers (18 self-formulated items), depressive symptoms (Beck Depression Inventory), perceived autonomy support (Modified Health Care Climate Questionnaire), and self-efficacy (Partners in Health Questionnaire). Factor analysis was used to identify barrier domains. Correlation coefficients were computed to examine relationships between barrier domains and patient characteristics.

Results

Nine barrier domains were identified. Barriers perceived as important were as follows: high sodium content in products, lack of sodium feedback, lack of goal setting and discussing strategies for sodium reduction, and not experiencing CKD-related symptoms (mean scores > 3.0 on 5-point scales, ranging from 1 'no barrier' to 5 'very important barrier'). Other barriers (knowledge, attitude, coping skills when eating out, and professional support) were rated as moderately important (rated around midpoint), and the barrier 'intrinsic motivation' was rated as somewhat important (mean score = 1.9). Sodium reduction barrier domains were not associated with gender and kidney function, but were associated with age, level of education, number of comorbidities, perceived autonomy support, depressive symptoms, and self-efficacy (range r = 0.17 - 0.35). Patients with lower self-efficacy and perceived autonomy support scores experienced most sodium reduction barriers.

Conclusions

Patients with CKD experience multiple important sodium reduction barriers and could benefit from support strategies that target various sodium reduction barriers and strengthen beliefs regarding self-efficacy and autonomy support. Additionally, environmental interventions should be implemented to reduce sodium levels in processed foods.

Introduction

In patients with chronic kidney disease (CKD), kidney function gradually and usually permanently declines over time. The severity of CKD can be classified into five stages, with CKD stage 5 as most advanced stage of CKD. In CKD stage 5, 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] In all stages of CKD, patients are being advised to reduce their sodium intake to a maximum of 2000 mg a day[2] because a reduction to the recommended amount of sodium has been associated with beneficial health outcomes, for example a decreased blood pressure.[3-5] In early stages of CKD, limiting sodium intake is considered especially important because it can contribute to slowing down disease progression towards ESKD and to reduce risks of cardiovascular complications.[6,7] Unfortunately, daily sodium consumption of most patients with CKD far exceeds the advised sodium intake,[5] and it seems that current health care does not provide patients with the necessary support to incorporate the sodium treatment guidelines into their daily life.

Literature suggests that in order to successfully limit dietary sodium in patients with CKD, behavioural support strategies are needed.[3,5] It has also been argued that individualization of support is vital, for instance by taking patients' perceived barriers into account.[8,9] However, to the best of our knowledge, there is a paucity of data on barriers regarding a low-sodium diet in patients with CKD, and the studies that have been conducted were performed in patients with ESKD (more specifically, in patients receiving haemodialysis).[10–12] Moreover, these studies focused on only a few sodium barriers; Clark-Cutaia et al. assessed the importance of three sodium barrier items (i.e., 'Sometimes I crave salty foods', 'Resisting salty foods where I work is difficult for me', and 'I have trouble keeping track of the amount of the nutrients that I eat from meal to meal [such as sodium, potassium, phosphorus]'[13])[10] and Agondi et al. and Welch et al. assessed the importance of five sodium barrier items (i.e., 'Eating a low salt diet makes it difficult to eat out', 'The food does not taste good in a low salt diet', 'It is expensive to follow a low salt diet', 'Following a low salt diet takes too long', and 'It is very difficult to understand how to follow a low salt diet').[11,12]

To increase our understanding of the sodium reduction barriers patients encounter in earlier stages of CKD (i.e., CKD stage 1 to 4), our study group conducted a qualitative study (i.e., focus groups with patients and health care professionals) and the results indicate that patients with CKD experience multiple barriers when reducing sodium, including a lack of intrinsic motivation, knowledge, personal goal setting and action planning, feedback, coping skills, and support.[14] This study provided in-depth knowledge about patients' experiences when reducing sodium, but further research is warranted to assess how common these identified barriers are in patients with CKD and to examine which barriers patients perceive as most important. Furthermore, the qualitative design is not suitable for assessing which factors are associated with sodium reduction barriers in order to identify patients that will benefit most from support strategies. Previous studies have shown that patients with ESKD who received haemodialysis treatment for a longer time experience more sodium reduction barriers[11] and that sodium intake is associated with age, gender, level of education, and comorbidities.[10,11,15,16] Additionally, literature suggests that psychosocial factors, such as depressive symptoms,[17] self-efficacy,[18,19] and support from health care professionals[18] are associated with treatment adherence in patients with ESKD, and hence, it is plausible that these factors are also related to difficulties with adhering to the sodium treatment guidelines.

Therefore, the objectives of this study were to assess the importance of previously identified sodium reduction barriers among patients with CKD stage 1 to 4, and to investigate whether sociodemographic, clinical, and psychosocial factors were associated with perceived sodium reduction barriers. This knowledge will enable us to develop individualized behavioural strategies to support patients with CKD in reducing sodium intake and consequently slow down disease progression towards ESKD.

Methods

Design and participants

Participants of this cross-sectional study were recruited between November 2013 and February 2014 from Leiden University Medical Centre in the Netherlands. Dutch speaking patients who were treated for their kidney disease by a nephrologist, and with a kidney function (estimated Glomerular Filtration Rate [eGFR]) of at least 20 mL/min/1.73 m^2 (i.e., no upper limit for eGFR), were eligible for inclusion. Patients in CKD stage 5 in need for or receiving kidney replacement therapy or conservative therapy (i.e., palliative care) were excluded to limit heterogeneity in treatment characteristics that may influence dietary behaviour. Eligible patients received a study invitation, detailed information explaining the procedure and confidentiality, an informed consent form (for study participation and medical data collection), a questionnaire, and a pre-stamped envelope. Participating patients returned the signed informed consent form and the completed questionnaire. Approval of the medical ethics committee was obtained (P10.056).

Measurements

After receiving signed informed consent forms, clinical data was collected from hospital information systems and medical records. The most recent medical measurements were included, given that measurements were conducted within the prior year. Kidney function was calculated using the abbreviated Modification of Diet in Renal Disease formula.[20] Sodium excretion (i.e., a measure for dietary sodium intake) and protein excretion were estimated from 24-hour urinary samples. The number of comorbidities was computed based on the presents of diabetes mellitus (type 1 or 2) and cardiovascular disease (cerebrovascular accident, coronary artery disease, and/or peripheral artery disease).

The questionnaire comprised items addressing patients' experiences with sodium reduction, and sociodemographic and psychosocial factors. Prior to usage, the questionnaire was pilot tested among nine patients, and revised based on feedback regarding acceptability and feasibility. Patients were asked whether they had received a sodium advice from professionals and whether they (had) tried to reduce their sodium intake. If patients indicated having experience with reducing sodium (i.e., irrespective of whether they succeeded), they were invited to fill out items regarding experiences with reducing sodium. The questionnaire also assessed perceived sodium adherence (single item using Visual Analogue Scale [VAS], ranging from 1 'never' to 10 'always') and perceived barriers for reducing sodium intake (using 18 self-formulated items based on a previous qualitative study,[14] rated on a five-point scale ranging from 1 'no barrier' to 5 'very important barrier'). A sum score of all sodium reduction barrier items was computed as indication for the amount of difficulties experienced. Depressive symptoms were measured using the Beck Depression Inventory (BDI).[21] The BDI contains 21 items using a four-point scale (0 - 3), and total scores ranged from 0 to 63, with higher scores indicating more depressive symptoms. The BDI proved to be reliable with a Cronbach alpha value of 0.88. Self-efficacy regarding self-management skills was assessed using the Partner in Health questionnaire (PIH)[22] and measured the following domains: knowledge of disease, active participating in decision-making, ability to monitor and manage symptoms, adopt a healthy lifestyle, and manage physical, emotional, and social consequences. A total score was calculated based on the sum of 13 items rated on a nine-point scale (ranging from 0 'very bad' to 8 'very good'). The total score ranged from 0 to 104, with a higher score indicating a higher self-efficacy. The PIH showed good reliability with a Cronbach alpha value of 0.89. Perceived autonomy support from health care professional was assessed using the Modified Health Care Climate Questionnaire (HCCQ).[23] Six items were rated on a seven-point scale (ranging from 1 'fully disagree' to 7 'fully agree'). A total score was computed by averaging item scores, and a higher score implied greater perceived support from professionals regarding being autonomous. The HCCQ showed good reliability with a Cronbach alpha value of 0.88.

Analysis

Descriptive statistics were computed for patient characteristics and sodium reduction barriers. Chi-square tests of association and t-tests were conducted to detect differences in patient characteristics between patients who were included in and excluded from analyses. For the purpose of data reduction, exploratory factor analysis (EFA) using varimax rotation was conducted to identify underlying sodium reduction barrier domains. The number of factors extracted was based on examination of a scree plot, Kaiser criterion (eigenvalues > 1), and the (theoretical) interpretability of the extracted factors. Furthermore, data was inspected for several standard indices to assess the factorability and the strength of the relationship among items, including sample adequacy (e.g., Kaiser-Meyer-Olkin measure > 0.50), sphericity (i.e., a significant Bartlett's test [p-value < 0.05]), common variance (i.e., communalities > 0.50), correlations (e.g., no multicollinearity) and factor loadings (e.g., minimum item loading of 0.30, and no or few cross-loadings [i.e., item loading of 0.32 or higher on two or more factors]).[24,25] Subscales were created by averaging items, and internal consistency was examined using Cronbach alpha measures.

Correlation coefficients were calculated to test associations between sodium reduction barriers (separate barrier domains and barrier sum score) and sociodemographic (age, gender, and level of education), clinical (kidney function and number of comorbidities), and psychosocial factors (perceived autonomy support, depressive symptoms, and self-efficacy): Pearson correlation coefficients for continuous factors and Point-biserial correlation coefficient for dichotomous factors. To avoid biased results and loss of power, missing data were imputed using multiple imputation (using 10 repetitions) – a recommended technique to deal with missing data in which plausible estimates are calculated based on known patient characteristics.[26,27]

Several sensitivity analyses were conducted to test the robustness of our results. First, analyses were repeated without imputing missing data. Second, Spearman's rank-order correlation coefficients were calculated to investigate if results would change when treating 'level of education' and 'number of comorbidities' (i.e., no comorbidity, 1 comorbidity, and 2 comorbidities) as ordinal variables (i.e., 6 education categories ranging from 'elementary education' to 'higher professional education/university' instead of 2 categories [low and high]). Third, t-tests and one-way analyses of variance (ANOVA Tukey post-hoc) were used to determine if barriers differed between categories of gender, level of education and number of comorbidities. Fourth, p-values of correlation coefficients were corrected for multiple testing using Benjamini and Hochberg False Discovery Rate.[28] Finally, to investigate if the amount of difficulties patients encounter when reducing sodium intake is also an indication of adherence to the sodium treatment guidelines, Pearson correlation coefficients were calculated for the associations between the barrier sum score and sodium adherence using objective (i.e., 24-hour urinary sodium excretion) and subjective (i.e., perceived sodium adherence) measures. All analyses were performed using SPSS version 24.0, and p-values of < 0.05 were considered statistically significant.

Results

Patient characteristics

The questionnaire was returned by 191 out of 323 patients (59.1%), after which 35 patients (18.3%) were excluded from analysis because they had no experience with reducing sodium intake or because only sociodemographic data was available (see Figure 1).

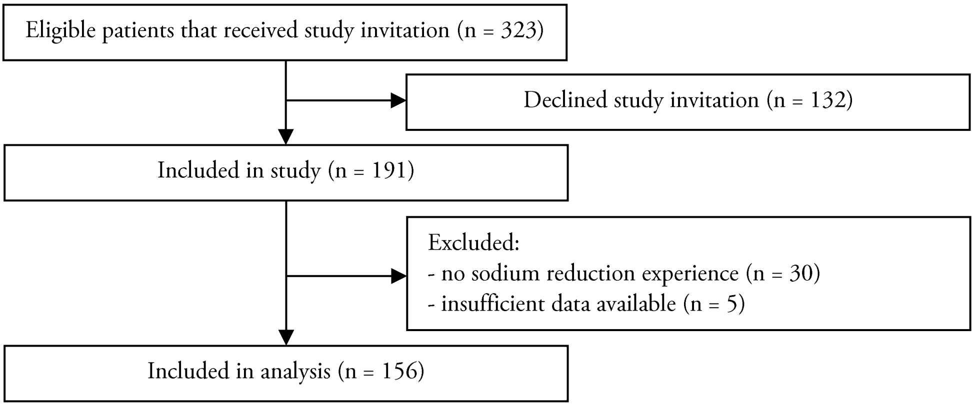

Figure 1. Flow diagram of the study

No significant differences in patient characteristics (see Table 1) were detected between patients who were included in and excluded from the analyses, with the exception that included patients had lower levels of haemoglobin (t = -2.3, p = .024), lower kidney function (t = -2.5, p = .019), and more often cardiovascular disease (χ^2 = 6.3, p = .012).

In the included sample of 156 patients, the mean (standard deviation [SD]) sodium excretion was 145.7 (60.1) mmol/24-hour, and patients gave themselves a mean (SD) mark of 6.6 (2.7) out of 10 on perceived sodium adherence. Table 1 depicts all patient characteristics.

Perceived sodium reduction barrier scores

Only four patients (2.6%) indicated that they experience no barriers when reducing sodium. The results showed that various sodium reduction barriers could be considered important (mean scores > 3.0 on a 5-point scale).

Table 1. Patient characteristics (N = 156) [a]

Characteristic	
Sociodemographic	
Age, years, mean ± SD	62.1 ± 13.6
Sex, male, n (%)	93 (59.6)
Ethnicity, Dutch, n (%) [*]	139 (89.1)
Married or cohabiting, yes, n (%)	118 (75.6)
Education, low, n (%) [**, b]	86 (55.1)
Paid work status, yes, n (%) [***]	53 (34.0)
Clinical [c]	
Primary cause of kidney failure, n (%) [□, d]	
Diabetes mellitus	5 (3.2)
Glomerulonephritis	44 (28.2)
Renal vascular disease	16 (10.3)
Other cause	79 (50.6)
Diabetes mellitus, n (%) [□]	27 (17.3)
Cardiovascular disease, n (%) [□]	50 (32.1)
Time on nephrology care, years, median (IQR) [□□]	4 (1-13)
Systolic blood pressure, mm Hg, mean ± SD [□□□]	134 ± 19
Diastolic blood pressure, mm Hg, mean ± SD [□□□]	79 ± 11
Use of antihypertensive medication, yes, n (%) [Δ]	123 (78.8)
Body Mass Index, kg/m^2, mean ± SD [ΔΔ]	27.1 ± 4.4
Haemoglobin, g/dL, mean ± SD [ΔΔΔ]	13.5 ± 1.6
eGFR, mL/min/1.73 m^2, mean ± SD [†]	47.6 ± 21.5
Protein excretion, g/24-hour, median (IQR) [‡]	0.3 (0.1-0.9)
Sodium [c]	
Sodium, mmol/24-hour, mean ± SD [‡, e]	145.7 ± 60.1
Perceived sodium adherence, mean ± SD [ϕ]	6.6 ± 2.7
Received sodium advice from professional, yes, n (%)	67 (42.9)
Psychosocial	
Perceived autonomy support, mean ± SD [ϕϕ]	5.8 ± 0.8
Self-efficacy, mean ± SD [ϕϕϕ]	73.7 ± 17.5
Depressive symptoms, mean ± SD [◊]	7.3 ± 6.4

Available for: [*]155 (99.4%), [**]154 (98.7%), [***]153 (98.1%), [□]144 (92.3%), [□□]140 (89.7%), [□□□]143 (91.7%), [Δ]127 (81.4%), [ΔΔ]111 (71.2%), [ΔΔΔ]115 (73.7%), [†]114 (73.1%), [‡]78 (50.0%), [ϕ]144 (92.3%), [ϕϕ]141 (90.4%), [ϕϕϕ]86 (55.1%), [◊]138 (88.5%) patients. [a] Continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables and as median (boundaries of interquartile range, IQR) for skewed variables. [b] Low education was classified as: primary education and lower secondary education. [c] Differences in time between completing the questionnaire and clinical measurements: mean (SD) of 0.5 (2.5) months for eGFR, mean (SD) of 1.7 (3.3) months for sodium excretion, mean (SD) of 1.6 (3.7) months for protein excretion, mean (SD) of 0.7 (0.9) for haemoglobin, median (IQR) of 3.6 (0.4 - 9.9) months for Body Mass Index, and median (IQR) of 0.2 (-1.3 - 3.3) months for blood pressure measurements. [d] Primary kidney disease was classified into four categories following the European Renal Association - Dialysis and Transplantation Association registry codes.[41] [e] Conversion factor for mmol/24-hour sodium excretion to mg/24-hour sodium excretion: x 23.

Patients had problems managing their low-sodium diet because many products contain (high levels of) sodium, they did not experienced CKD-related symptoms, they lack feedback on their sodium intake, and they did not set personal sodium goals and discuss strategies on how to reduce sodium with professionals. Sodium reduction barriers that were considered somewhat important were motivation-related barriers (mean scores ≤ 2.0), indicating that patients did not experience difficulties because they believe reducing sodium is not beneficial for them personally or their health. The remaining nine barriers items were rated as moderately important (mean scores ranging from 2.2 to 2.8). Table 2 contains scores of all barrier items.

Perceived sodium reduction barrier domains

The EFA showed a nine factor solution, explaining 81.8% of the variance. Overall, indicators showed that our data was suitable for factor analysis: no multicollinearity was detected, Kaiser-Meyer-Olkin exceeded the minimum of 0.50 (value = 0.63), Bartlett's test of sphericity was significant (p = .000), and communalities were greater than 0.50 (mean value = 0.82). Seven domains with adequate eigenvalues (> 1) were created that consisted of multiple items with high item loadings (i.e., ranging from 0.62 to 0.92): attitude (4 items), professional support (2 items), symptoms (2 items), knowledge (2 items), intrinsic motivation (2 items), feedback (2 items), and goal and strategy (2 items). The domains also showed moderate to good reliability with Chronbach alpha values ranging from 0.62 to 0.87.

The interpretation of the two remaining factors was less clear with freestanding items assessing the barriers 'sodium in products' and 'coping skills when eating out', and with borderline cross-loading detected in the latter barrier (i.e., with the domain 'attitude'). Solutions were examined, but did not change the results. Due to the nature of this EFA (i.e., data reduction in light of correlation analysis), and the importance of both items (mean scores were 2.8 for 'coping skills when eating out' and 3.5 for 'sodium in products'), the decision was made to treat these single items as separate barrier domains. The barrier 'sodium in products', however, was excluded from the correlation analysis because sodium content of products cannot be modified by patients, and hence, is most likely not associated with patient characteristics. Table 2 depicts all barrier domains and Chronbach alpha values.

Table 2: Descriptives of sodium reduction barrier items, domains, sum score, and Chronbach alpha values (N = 156) [a, b]

Sodium reduction barriers	**Mean (SD)**
Attitude (α = 0.63) [□]	2.5 (0.8)
Low-sodium food taste bad	2.7 (1.2)
A low-sodium diet is unsocial	2.4 (1.1)
A low-sodium diet is time and energy consuming	2.3 (1.1)
Low-sodium products are expensive	2.6 (1.2)
Symptoms (α = 0.86) [□□]	3.2 (1.2)
Not feeling ill	3.3 (1.2)
No CKD-related symptoms	3.0 (1.2)
Professional support (α = 0.87) [□□□]	2.5 (0.9)
Health care professionals are not patient-centred enough	2.4 (0.9)
Health care professionals have insufficient time to support me	2.6 (0.9)
Knowledge (α = 0.75) [Δ]	2.3 (0.9)
Insufficient knowledge on how to reduce sodium intake	2.2 (1.0)
Insufficient knowledge about sodium content in products	2.4 (1.0)
Intrinsic motivation (α = 0.83) [□□]	1.9 (0.8)
A low-sodium diet is not beneficial for my health	1.9 (0.9)
A low-sodium diet is not important for me personally	2.0 (0.8)
Feedback (α = 0.70) [ΔΔ]	3.1 (1.1)
Insufficient insight into my daily sodium intake	3.3 (1.2)
Receiving insufficient feedback on my sodium intake	3.0 (1.2)
Goal and strategy (α = 0.62) [ΔΔ]	3.4 (1.0)
No personal and concrete goals have been set to reduce my sodium intake	3.1 (1.2)
No sodium reduction strategies has been discussed with my professional	3.7 (1.1)
Coping skills when eating out [ΔΔΔ]	
Difficult to refuse food at parties and when eating out	2.8 (1.2)
Sodium in products [□□□]	
The majority of products contain (high levels of) sodium	3.5 (1.2)
Barriers sum score (α = 0.79) [c]	49.5 (9.2)

[a] Data available between 135 (86.5%) and 147 (94.2%) patients for each single barrier. Data of domains available for the following: [□]143 (91.7%), [□□]139 (89.1%), [□□□]129 (82.7%), [Δ]137 (87.8%), [ΔΔ]141 (90.4%), [ΔΔΔ]135 (86.5%). Possible range is 1 - 5, with 1 indicating 'no barrier' and 5 'very important barrier'. [b] Loadings were strong for primary items in the domains 'attitude' (0.88, 0.78, 0.62, and 0.86, respectively), 'symptoms' (0.91 and 0.91), 'professional support' (0.90 and 0.92), 'knowledge' (0.83 and 0.90), 'intrinsic motivation' (0.91 and 0.88), 'feedback' (0.76 and 0.84), 'goal and strategy' (0.84 and 0.87), 'coping skills when eating out' (0.53), and 'sodium in products' (0.82) – all other item loadings on the factors were well below 0.40. [c] Barrier sum score was calculated when all barriers data were available (n = 111, 71.2%). Possible score range is 18 - 90, with higher scores indicating more difficulties with reducing sodium intake.

Factors associated with perceived sodium reduction barrier domains

The correlation coefficients showed that several sociodemographic, clinical and psychosocial factors were associated with sodium reduction barrier domains (see Table 3). First, associations were found between self-efficacy and the barriers 'knowledge', 'attitude', and 'feedback': patients who believed to a lesser extent that they are capable of managing their disease reported more often that a lack of knowledge was a barrier to reduce sodium intake (p = .006), expressed a more negative attitude towards limiting sodium (p = .036), and more often considered a lack of feedback as a barrier (p = .049). Associations were also found between age, the number of comorbidities, depressive symptoms, and the barrier 'symptoms': older patients, patients with more comorbidities, and patients with less depressive symptoms more often reported that not experiencing CKD-related symptoms was a barrier for reducing sodium (p = .015, p = .027, and p = .007, respectively). Furthermore, age and level of education were associated with the barrier 'goal and strategy': younger patients and patients with high levels of education more often considered a lack of setting goals and planning strategies as a barrier for reducing sodium (p = .012 and p = .003). The barrier 'coping skills when eating out' was associated with number of comorbidities and self-efficacy: a lack of skills when eating out as barrier for reducing sodium was more often mentioned by patients with more comorbidities (p = .035), and by patients who believe to a lesser extent they are capable to manage their disease (p = .044). Furthermore, associations were also found between the barrier 'professional support', perceived autonomy support and self-efficacy: patients who experienced insufficient professional support as a barrier believed to a lesser extent that they receive sufficient autonomy support from professionals and believed to a lesser extent that they are capable to manage their disease (p < .001 and p = .005). No factors were associated with the barrier 'intrinsic motivation', and gender and kidney function were not related to barrier domains. Finally, perceived autonomy support and self-efficacy were associated with the barrier sum score: patients who believed to a lesser extent that they receive sufficient autonomy support from professionals and patients who believed to a lesser extent that they are capable to manage their disease, experienced more barriers when limiting sodium intake (p = .032 and p = .013).

Table 3: Correlation coefficients for perceived sodium reduction barriers and sociodemographic, clinical and psychosocial characteristics (N = 156)

Barriers	Age[a]	Gender[b]	Level of edu-cation[b]	Number of comor-bidities[a]	eGFR[a]	Autonomy support[a]	Depressive symptoms[a]	Self-efficacy[a]
Attitude	-.06	.17	-.07	.10	-.02	-.01	.08	-.18*
Symptoms	.21*	-.01	.11	.19*	-.16	-.02	-.25**	-.09
Professional support	-.02	.07	.05	.04	.00	-.35**	.09	-.25**
Knowledge	-.07	.03	-.04	.08	.04	-.10	.06	-.25**
Intrinsic motivation	-.10	-.04	.11	-.18	.12	-.13	-.11	-.06
Feedback	-.16	.10	-.01	.11	.00	-.15	.03	-.17*
Goal and strategy	-.24*	-.03	.25**	-.03	.13	-.12	-.06	.11
Coping skills eating out	-.05	.08	-.02	.19*	.12	-.14	.09	-.19*
Barriers sum score	-.10	.03	.09	.11	.03	-.21*	-.06	-.24*

[a] Pearson correlation coefficients. [b] Point-biserial correlation coefficients for gender and level of education (categories were low and high level of education). * $P < 0.05$, ** $P < 0.01$.

Sensitivity analysis

The sensitivity analysis showed that the majority of the results remained stable when conducting complete case analysis, with the exception that no significant relationships were found between self-efficacy and the barriers ‘attitude’ and ‘coping skills when eating out’ (r = -0.16 [*p* = .164] and r = -0.19 [*p* = .097]). However, a significant association was now found between perceived autonomy support and the barrier ‘coping skills when eating out’ (r = -0.18, *p* = .041). Furthermore, compared to the main analysis, similar results were found when calculating Spearman's rank-order correlation coefficients for associations between sodium reduction barriers, level of education and number of comorbidities on a ordinal level (data not shown). The t-tests revealed that patients with high levels of education believed to a higher extent that not setting goals and discussing strategies are important barriers compared to patients with low levels of education (mean [SD] of 3.7 [0.8] compared to 3.2 [1.0], *p* = .003), and revealed that none of the barriers differed between men and women (data not shown). The ANOVA’s showed that there was an association between the number of comorbidities and the barrier ‘symptoms’ (F = 4.1 [2, 154], *p* = .017), and post-hoc comparison indicated that patients with two comorbidities believed to a higher extent that not experiencing CKD-related symptoms is an important barrier compared to patients with no comorbidities (mean [SD] was 3.8 [1.0] compared to 2.7 [1.2], *p* = .013).

Furthermore, after correction for multiple testing two associations remained significant: level of education was associated with the barrier ‘goal and strategy’ (p = .036), and perceived autonomy support was associated with the barrier ‘professional support’ (p < .001). Only trends were now observed for associations between self-efficacy and the barriers ‘knowledge’ (p = .060), and ‘professional support’ (p = .055), and between depressive symptoms and the barrier ‘symptoms’ (p = .065). Finally, the analyses showed that the barrier sum score was associated with perceived sodium adherence (r = -0.53, p < .001, n = 109), but not with 24-hour urinary sodium excretion (r = 0.03, p = .811, n = 60).

Discussion

This study has shown, in accordance with previous studies,[10–12,14,29] that patients with CKD perceive adhering to a low-sodium diet as a difficult task. They regard multiple barriers to be important when reducing sodium: patients believed to a high extent that reducing sodium is difficult because many products contain (high levels of) sodium, they do not experience CKD-related symptoms, lack feedback on sodium intake, and do not set sodium goals and discuss strategies for reducing sodium with professionals. Patients also believed to a moderate extent that reducing sodium is difficult because they have insufficient knowledge on how to reduce sodium intake, lack the skills to refuse food when eating out, receive insufficient support from professionals, and perceive a low-sodium diet as untasteful, unsocial, expensive, and time and energy-consuming. Finally, most patients did not experience difficulties because they believe that reducing sodium intake is not beneficial for them personally or for their health. Direct comparison with literature is difficult because previous studies assessed the importance of only a few sodium reduction barriers in patients with ESKD (more specifically, in patients receiving haemodialysis).[10–12] However, barrier items included by Agondi et al. and Welch et al. partially overlap with items of our domains ‘attitude’, ‘knowledge’, and ‘coping skills when eating out’.[11,12] Comparison of mean scores on these items suggests that in all three studies many patients believed to a moderate extent that reducing sodium is difficult because it is time-consuming and expensive, and they lack knowledge on how to reduce sodium (i.e., items rated around midpoint). However, patients in our study believed to a lesser extent that a bad taste of low-sodium food makes it difficult to adhere to a low-sodium diet (2.7 versus 3.8 and 3.3)[11,12] and they reported less problems with adherence when eating out (2.8 versus 3.7).[11] Although all studies specifically address sodium barriers, higher scores in previous studies could be explained by the patient population: patients receiving haemodialysis have additional diet restrictions (e.g., protein and potassium restrictions), and hence, restrict patients even more in choosing and cooking healthy but also tasty food. Finally, previous studies did not assess barriers related to motivation; however, they did assess patients beliefs about benefits of a low-sodium diet.[11,12] They found that patients with ESKD believed to a high extent that a low-sodium diet is good for their health, which corresponds with our finding that patients do not experience difficulties because they think it is not beneficial for their health.

We also identified patient characteristics that were related to barriers for adhering to a low-sodium diet. Various sodium reduction barriers (i.e., a negative 'attitude', and a lack of 'knowledge', 'symptoms', 'goal setting and discussing strategies', 'feedback', 'coping skills when eating out', and 'professional support') were associated with patient characteristics, namely age, level of education, depressive symptoms, number of comorbidities, perceived autonomy support, and self-efficacy. Furthermore, patients who believed to a lesser extent that they are capable to manage their disease and patients who believed to a lesser extent they receive sufficient autonomy support from professionals, experienced more barriers when limiting dietary sodium. These findings suggest that patients differ in the extent to which they experience barriers when striving to adhere to a low-sodium diet. Hereby, this study adds to previous studies that found these sociodemographic and clinical factors associated with sodium excretion[10,11,15,16] and found these psychosocial factors associated with treatment adherence in patients with ESKD.[17–19] Furthermore, the factor that was most consistently related to sodium reduction barriers was self-efficacy, and these findings are in line with a previous study by Curtin et al., who found patients' self-efficacy, compared to demographic and health-related factors, to be most consistently related to self-management behaviour in patients with CKD.[30]

To the best of our knowledge, this is the first study to assess the importance of perceived sodium reduction barriers in an early stage of CKD and to identify which patients could benefit most from support strategies. Other strengths of this study are that barrier items in the questionnaire were based on a previous qualitative study[14] and that the questionnaire included a broad range of sodium reduction barriers and showed moderate to good psychometric qualities. However, before this questionnaire can be used in practice to identify sodium reduction barriers in individual patients, additional research is needed (e.g., conducting a confirmative factor analysis in a larger population or executing a longitudinal study to evaluate the test-retest reliability). A limitation of this study is that the date of clinical measurements did not coincide with the date questionnaires were filled out. However, we do not believe this led to biased results as the mean (SD) difference between kidney function measurements and completing the questionnaire was 0.5 (2.5) months and it is expected that kidney function will be constant in this short period of time. There was also missing data, for example because patients did not fully complete the questionnaire, patients did not gave permission to collect medical data, or clinical measurements were not conducted within the prior year. However, the majority of the results prior and after imputations were similar and few differences were detected between patients who were included in and excluded from analyses, and therefore, it is unlikely that missing data led to biased results. Furthermore, the sensitivity analysis showed that the barrier sum score was associated with perceived sodium adherence, but not with 24-hour urinary sodium excretion. Explanations for these findings could be that limited data on sodium excretion was available (50%), and that we used a single sodium measurement[9] that was measured on a date that do not coincide with the date questionnaires was filled out (mean [SD] difference was 1.7 [3.3] months). Finally, although our response rate of 59.1% is similar to the average response rate of 65% for postal questionnaires in health care settings,[31] it should be noted that our results may not be fully representative of the broad population of patients with CKD.

Taken together, the results of this study suggest that patients with CKD believed to a relatively high extent that limiting dietary sodium is beneficial, but still experience multiple barriers when reducing sodium intake. Therefore, solely educating patients about the benefits of sodium reduction will be insufficient but a multifaceted approach that target various important barriers is required to provide patients with the support they need to incorporate the sodium treatment guidelines into their daily life. The findings also suggest that patients who believed to a lesser extent that they are capable to manage their disease and receive sufficient autonomy support from professionals, experienced more sodium reduction barriers, and thus, support strategies should also strengthen beliefs regarding self-efficacy and autonomy. The need for such a multifactorial approach to support patients with the complex task of successful behaviour change is in line with literature suggesting that theory-based self-regulation interventions that encompass multiple behaviour change techniques are required.[32–35] Based on our findings, we believe that in particular, the following strategies could be of use. First, professionals could use the patient-centred techniques of motivational interviewing to elicit behaviour change, increase autonomy support and strengthen patients' self-efficacy.[36,37] Additionally, it may provide a solution for the barriers 'professional support' and 'goal and strategy', as shared decision making, goal setting and discussing action plans are key elements of motivation interviewing.[36] Second, coaching is considered important in behaviour change,[38] and continuous support and guidance from professionals could increase self-efficacy and knowledge of patients. Third, an intervention comprising educational cooking sessions successfully reduced sodium intake in patient with CKD[39] and could increase patients' practical knowledge and skills on how to reduce sodium and positively change attitudes (i.e., cooking flavorful dishes that take little time and are inexpensive). Fourth, self-monitoring has been identified as a key element for successful behaviour change,[32,34] and stimulating patients to engage in self-monitoring (e.g., sodium intake by means of an online food diary and home-based blood pressure measurements) could give patients direct feedback on their sodium intake and disease progression. Fifth, sodium content of products and eating out were identified as important barriers, and hence, environmental interventions should be implemented as well (e.g., reducing sodium content in processed and catered foods).[40] Finally, future studies are needed to investigate whether the suggested strategies can indeed help patients to reduce sodium intake and improve health outcomes in patients with CKD.

Conclusions

Patients with CKD experience multiple important barriers when reducing sodium intake, especially patients with lower self-efficacy. Addressing perceived sodium reduction barriers could be a starting point for interventions to support patients with CKD in reducing sodium intake and consequently slow down disease progression towards ESKD.

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Chapter 4

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

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Abstract

Background

To evaluate the effectiveness and sustainability of self-managed sodium restriction in patients with chronic kidney disease.

Study design

Open randomised controlled trial.

Setting and participants

Patients with moderately decreased kidney function from 4 hospitals in the Netherlands.

Intervention

Regular care was compared with regular care plus an intervention comprising education, motivational interviewing, coaching, and self-monitoring of blood pressure (BP) and sodium.

Outcomes

Primary outcomes were sodium excretion and BP after the 3-month intervention and at 6-month follow-up. Secondary outcomes were protein excretion, kidney function, antihypertensive medication, self-efficacy, and health-related quality of life (HRQOL).

Results

At baseline, mean ± standard deviation (SD) sodium excretion rate was 163.6 ± 64.9 mmol/24-hour; mean estimated glomerular filtration rate was 49.7 ± 25.6 mL/min/1.73 m^2; median (boundaries of interquartile range [IQR]) protein excretion rate was 0.8 (0.4 - 1.7) g/24-hour; and mean 24-hour ambulatory systolic and diastolic BPs were 129 ± 15 and 76 ± 9 mm Hg, respectively. Compared to regular care only (n = 71), at 3 months, the intervention group (n = 67) showed reduced sodium excretion rate (mean change, -30.3 [95% CI, -54.7 to -5.9] mmol/24-hour), daytime ambulatory diastolic BP (mean change, -3.4 [95% CI, -6.3 to -0.6] mm Hg), diastolic office BP (mean change, -5.2 [95% CI, -8.4 to -2.1] mm Hg), protein excretion (mean change, -0.4

[95% CI, -0.7 to -0.1] g/24-hour), and improved self-efficacy (mean change, 0.5 [95% CI, 0.1 to 0.9]). At 6 months, differences in sodium excretion rates and ambulatory BPs between the groups were not significant, but differences were detected in systolic and diastolic office BPs (mean changes of -7.3 [95% CI, -12.7 to -1.9] and -3.8 [95% CI, -6.9 to -0.6] mm Hg, respectively), protein excretion (mean change, -0.3 [95% CI, -0.6 to -0.1] g/24-hour), and self-efficacy (mean change, 0.5 [95% CI, 0.0 to 0.9]). No differences in kidney function, medication, and HRQOL were observed.

Limitations

Nonblinding, relatively low response rate, and missing data.

Conclusions

Compared to regular care only, this self-management intervention modestly improved outcomes, although effects on sodium excretion and ambulatory BP diminish over time.

Introduction

Striving for a maximum daily sodium intake of 2000 mg is an important treatment goal in patients with chronic kidney disease (CKD)[1] because it can improve health outcomes.[2,3] However, despite the efforts of health care professionals, most patients with CKD do not reach the recommended sodium intake.[4]

Nonadherence to the sodium treatment guidelines seems to be a complex problem because previous studies have shown that patients with CKD face multiple barriers when reducing sodium intake,[5,6] including insufficient motivation, knowledge, feedback, coping skills, and personal goal setting. Hence, to successfully change lifestyle, theory-based self-regulation interventions that encompass multiple behaviour change techniques are required.[7-11] However, such self-management interventions to support patients with CKD to overcome these barriers and incorporate the sodium guideline into their daily lives are lacking.

Until now, mostly crossover trials have been conducted; these studies have shown that if patients with CKD adhere to a low-sodium diet, important risk factors for disease progression can be reduced,[12,13] including blood pressure (BP) and protein excretion.[14-17] However, these studies did not include behavioural approaches needed for long-term adherence and only evaluated efficacy directly after relatively brief (2 - 6 weeks) and strictly regulated interventions. Hence, they do not provide information about the effectiveness and sustainability of sodium interventions to support patients in real-life settings.

To our knowledge, there are only two pragmatic trials that included 24-hour urinary sodium excretion as an outcome parameter (i.e., the gold standard[18]). First, de Brito-Ashurst et al.[19] reduced sodium intake by means of educational cooking sessions, but only evaluated effects immediately after the intervention. Second, the Multifactorial Approach and Superior Treatment Efficacy in Renal Patients With the Aid of Nurse Practitioners Study (MASTERPLAN) study aimed at strict implementation of multiple treatment guidelines with the aid of nurse practitioners, which led to increased medication adherence, but did not improve lifestyle adherence.[20] Moreover, both interventions lacked a theoretical basis, were mainly education based, and included only a few behaviour change techniques.

Therefore, we designed a 3-month self-management intervention based on self-regulation theory, encompassing various evidence-based behaviour change techniques[7-11,21,22] to support patients with CKD in reducing their daily sodium intake. The aim of this Effects of Self-monitoring on Outcome of Chronic Kidney Disease (ESMO) trial was to investigate whether the intervention would result in reduced sodium intake and improved health outcomes (e.g., BP and protein excretion) directly after the 3-month intervention and at the 6-month follow-up. In addition, because the literature has shown that self-management interventions can improve patients' well-being, this study also aimed to improve health-related quality of life (HRQOL)[23] and self-efficacy (i.e., confidence in ability to manage the disease).[24]

Methods

Study design

This open randomised controlled trial was conducted from June 2011 to August 2014 at the nephrology departments of 3 university hospitals and 1 general teaching hospital in the Netherlands: Leiden University Medical Centre, University Medical Centre Groningen, Academic Medical Centre Amsterdam, and Sint Antonius Hospital Nieuwegein. Written informed consent was obtained from all participants before inclusion. This study was approved by the medical ethics committees of all centres (P10.056) and complies with the Declaration of Helsinki. The CONSORT (Consolidated Standards of Reporting Trials) checklist was used as reference for reporting.[25]

Participants and randomization

From June 2011 through March 2014, patients with moderately decreased kidney function and hypertension were recruited (Box 1 depicts all inclusion and exclusion criteria). Eligible patients received an invitation, information regarding the procedure and confidentiality, an informed consent form, and a baseline questionnaire. Upon receiving patients' written informed consent at the external data management centre (Nefrovisie), a medical information specialist allocated patients to the intervention or control condition using a computer-based block randomization procedure. The number of patients in each condition was predefined, and different sizes of blocks were used to prevent too many patients being consecutively assigned to the same condition. Only the medical information specialist knew the block sizes. Thereafter, researchers and patients were notified of the allocation.

Box 1. Inclusion and Exclusion Criteria

Inclusion criteria

- Dutch speaking
- ≥ 18 years
- Being treated by an internist
- Kidney function (eGFR) ≥ 20 mL/min/1.73 m^2
- Protein excretion measurements > 0.2 g/L or 0.3 g/24-hour
- 2 recent sodium excretion measurements ≥ 120 mmol/24-hour
- BP > 135/85 mm Hg or controlled BP with the use of antihypertensive medication, among which at least 1 RAAS blockade

Exclusion criteria

- BP >180/100 mm Hg or < 125/75 mm Hg
- Received a kidney transplant < 1 year ago
- Diagnosed with type 1 diabetes mellitus
- Had acute kidney failure
- Accelerated kidney function decrease ≤ 6 mL/min/1.73 m^2 in previous year
- Had a cardiovascular event (i.e., myocardial infarction or cerebrovascular event) < 6 months ago
- Diagnosed with malignancy < 5 years ago (other than basal cell or squamous cell carcinoma of skin)
- Participating in other clinical trial that included medication

Note: Inclusion and exclusion criteria as approved by the medical ethics committee and described in the Netherlands Trial Registry (study number: NTR2917). Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.

Study protocol

Both groups received regular care according to the Dutch Federation of Nephrology treatment guidelines[1] (based on the KDOQI [Kidney Disease Outcomes Quality Initiative][26] and KDIGO [Kidney Disease Improving Global Outcomes] guidelines[27]). Regular care consisted of consultations with the nephrologist every 3 to 6 months and, if necessary, nutrition counselling by a dietician. Those who received only regular care were the control group.

Patients in the intervention group also received the 3-month self-management intervention. During the intervention, patients were coupled with one of 4 personal coaches: 3 health psychologists and 1 dietician, all trained in motivational interviewing techniques.[28] The intervention started with a 1-hour individual motivational interview at the patient's hospital, which focused on discussing barriers, benefits, and strategies for sodium reduction; setting personal sodium goals; and strengthening intrinsic motivation and self-efficacy. Thereafter, patients received education, a kidney-friendly cookbook, and instructions for self-monitoring BP (using a Microlife WatchBP Home device), dietary intake (using an online food diary; www.mijnnierinzicht.nl by Bonstato), and 24-hour urinary sodium excretion (using an innovative point-of-care chip-device [Medimate BV]).[29] Patients were instructed to take measurements at least once a week in the first 6 weeks and, depending on patients' preferences, thereafter once every 2 or 3 weeks. Following these self-monitoring measurements (i.e., with the same frequency), patients received feedback by telephone from their coach and discussed progression, achievements, barriers, and possible solutions. After 3 months, a final motivational interview took place that focused on evaluation and relapse prevention. For a detailed intervention description following the Coventry, Aberdeen and London Refined (CALO-RE) taxonomy of behaviour change techniques,[30] see Items S1. Finally, if desired, patients received information regarding social support, refusal skills, medication adherence strategies, physical exercise, healthy eating, smoking, and alcohol intake.

Measurements and outcomes

Data acquisition

Data were collected at baseline, directly after the 3-month intervention, and at the 6-month follow-up. Sociodemographic, anthropometric, and medical data were collected during hospital visits by individuals not blinded to treatment allocation, using a secured online Case Report Form. Biochemical data were extracted from hospital information systems. Psychosocial measures were acquired using self-report questionnaires. All data were collected and stored on a secured server under administration of the data management centre.

Primary outcomes

Sodium intake was estimated from 24-hour urinary sodium excretion. BP was measured with ambulatory BP monitoring using validated Spacelabs 90207 and 90217 devices. Monitors were programmed for 24-hours with 15-minute day intervals and 30-minute night intervals. Recordings were corrected for patients' sleep-wake rhythm and considered satisfactory when meeting criteria of the European Society of Hypertension guidelines.[31] Office BP was measured by taking the average of 3 measurements using Microlife WatchBP Home after 5 minutes of rest.

Secondary outcomes

Because clinicians use different measures for kidney function, kidney function was measured as creatinine clearance corrected for body surface area (using the DuBois and DuBois formula[32]) and estimated glomerular filtration rate (using the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation[33]). Protein excretion was measured using 24-hour urinary protein excretion, and antihypertensive medication use was calculated by taking a sum score of the number of antihypertensive medications. HRQOL was assessed with the 36-item Short Form Health Survey.[34] Scores for physical and mental HRQOL ranged from 0 to 100, with higher scores indicating better HRQOL. The questionnaire showed good reliability, with Cronbach alpha values of 0.92 and 0.82 for physical and mental HRQOL, respectively. Furthermore, self-efficacy was assessed by the Chronic Disease Self-Efficacy Scales Manage Disease in General Scale.[35] Scores ranged from 1 to 10, with higher scores indicating a stronger belief in the capability of managing the disease. This questionnaire also showed good reliability, with a Cronbach alpha value of 0.73. In addition, because body weight is often reduced after sodium interventions,[15,36] body weight was also measured with shoes removed using the hospitals' calibrated digital scales.

Power calculation and statistical analysis

To detect a difference of 4 mm Hg in 24-hour systolic BP,[37] with an estimated standard deviation of 7 mm Hg,[38] a 2-sided significance of 0.05, and a power of 90%, 64 patients were needed in each group. Taking into account a dropout rate of 15%, we aimed to include 150 patients. Descriptive statistics were computed to describe baseline characteristics. To investigate the effectiveness of the intervention, we focused on the effect of the study group over time using intention-to-treat analysis and linear mixed modelling. Assumptions for linear mixed modelling were valid for all outcomes. Models included the following fixed variables: group, time, and the various continuous dependent variables. Furthermore, models included patient-level random effects to account for correlation between patients' repeated measures over time. An interaction term was also included as fixed variable: group * time, which indicated the effect (i.e., change in scores for dependent variables) of the study group by time. To increase the precision of our estimates, models were adjusted for the baseline value. Because a linear mixed model takes into account missing outcomes but not missing covariates, missing baseline values were imputed using multiple imputation (using 10 repetitions) because we do not believe "missing not at random" was dominant.[39] Several sensitivity analyses were performed to test the robustness of our results (see Item S1; including primary analysis adjusted for baseline covariates, without adjustments, and as-treated analysis). Statistical analysis was performed using SPSS, version 22.0 (IBM).

Results

Participant flow

In total, 151 of 333 (45.3%) eligible patients provided written informed consent. Hereafter, 138 patients started the allocated group and 26 patients dropped out during the trial, leaving 112 (74.2%) patients who completed the allocated group. In total, 138 patients were included in the primary intention-to-treat analysis: 67 patients in the intervention group and 71 patients in the control group. Figure 1 depicts the participant flow.

Baseline characteristics

In this sample of 138 patients, mean estimated glomerular filtration rate was 49.7 ± 25.6 (standard deviation) mL/min/1.73 m^2 and median protein excretion rate was 0.8 (boundaries of interquartile range, 0.4 - 1.7) g/24-hour. In addition, mean 24-hour ambulatory systolic and diastolic BPs were 129 ± 15 and 76 ± 9 mm Hg, respectively, and mean sodium excretion rate was 163.6 ± 64.9 mmol/24-hour (see Table 1). Various differences between the intervention and control groups were observed (see Item S2).

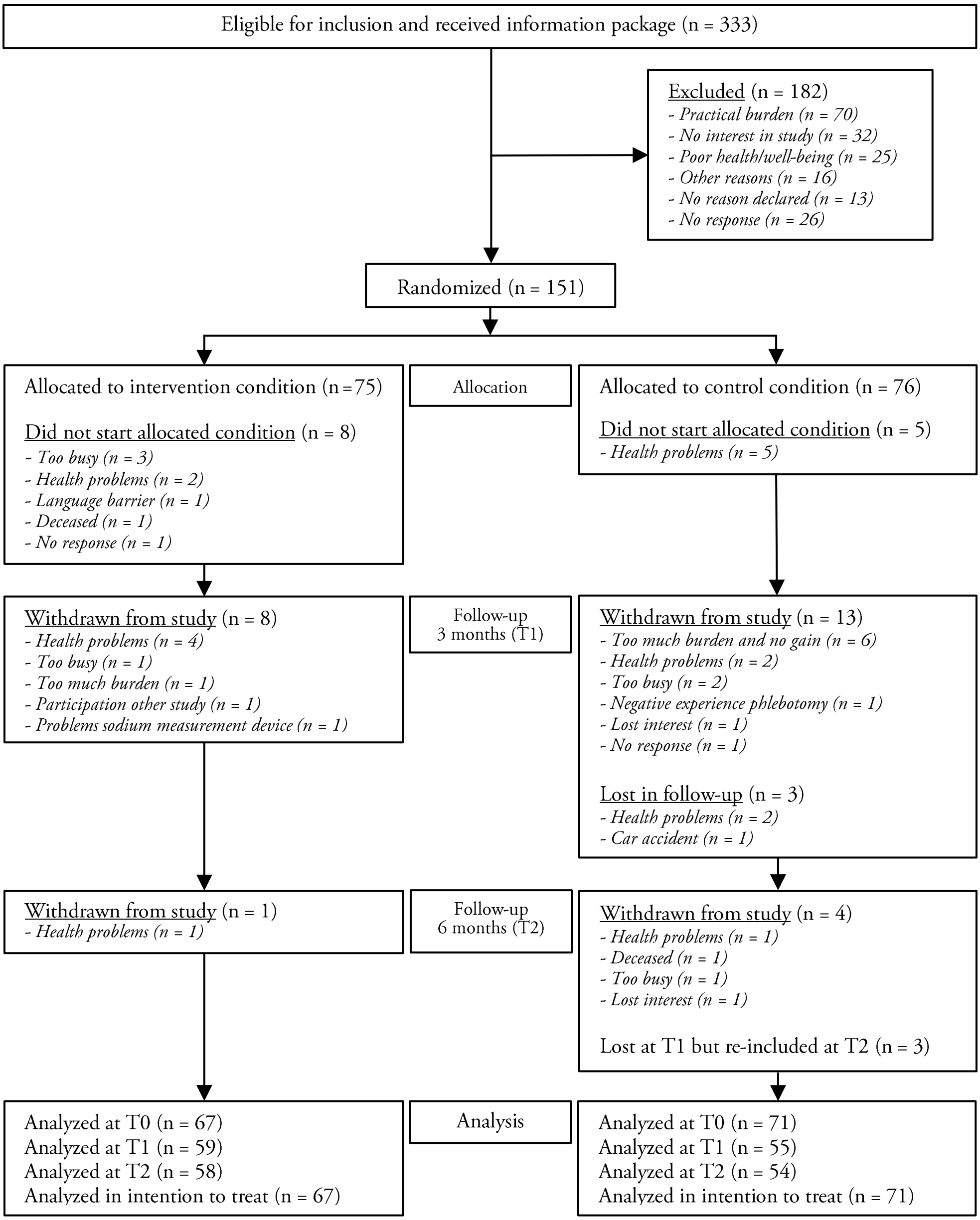

Figure 1. Participant flow

Patient adherence, goals, and evaluation

In total, 55 patients (82.1%) received the intervention according to protocol. Four (6%) patients did not attend the final interview, and 8 (12%) patients did not attend the final interview and had fewer than 5 self-monitoring moments and consultations. In addition to setting personal sodium goals, 21 (31%) patients set weight-loss goals, 9 (13%) patients set exercise goals, 1 (2%) patient set a goal to reduce alcohol intake, and 3 (5%) patients wanted to receive information regarding medication adherence strategies, social support, or refusal skills.

Patient satisfaction with the intervention was high: 42 (63%) patients returned the evaluation questionnaire and gave the intervention a mean score of 7.9 ± 0.9 on a 10-point scale, with higher scores indicating greater satisfaction. All separate intervention components (i.e., education, motivational interviews, feedback consultations, and self-monitoring tools) were evaluated as very useful: mean scores ranged from 4.0 ± 0.7 to 4.7 ± 0.6 on a 5-point scale, with higher scores indicating greater usefulness. It is important to note that although the food diary and sodium measurement device were evaluated as very useful, patients also had some frustration (both mean scores were 2.3 ± 1.5 on a 5-point scale [higher scores indicate higher levels of frustration]), which referred to the complexity of completing the food diary and to failures of the sodium measurement device (which meant that the procedure had to be repeated and, in a few cases, 24-hour urine had to be collected again or the device had to be replaced).

Primary and secondary outcomes

At three months

Several significant differences were observed at the end of the intervention (see Table 2). Compared to regular care alone, the intervention resulted in a -30.3 (95% confidence interval [CI], -54.7 to -5.9) mmol/24-hour mean change in sodium excretion rate, -3.4 (95% CI, -6.3 to -0.6) mm Hg mean change in daytime diastolic BP, -5.2 (95% CI, -8.4 to -2.1) mm Hg mean change in diastolic office BP, and -0.4 (95% CI, -0.7 to -0.1) g/24-hour mean change in protein excretion rate. Furthermore, there was a 0.5 (95% CI, 0.1 to 0.9) mean increase in self-efficacy score in the intervention group compared to the control group.

Table 1. Baseline patient characteristics (N = 138)

Characteristic	**Intervention (n = 67)**	**Control (n = 71)**
Demographic		
Age, years, mean ± SD	55.6 ± 11.7	54.7 ± 16.0
Gender, male, n (%)	53 (79.1)	60 (84.5)
Ethnicity, Dutch, n (%)	59 (88.1)	66 (93.0)
Married or cohabiting, n (%)	59 (88.1)	53 (74.6)
Education, low, n (%)	40 (59.7)	48 (67.6)
Paid job, n (%)	37 (55.2)	35 (49.3)
Clinical		
Primary cause of kidney failure, n (%) [a]		
Diabetes mellitus	6 (9.0)	2 (2.8)
Glomerulonephritis	16 (23.9)	14 (19.7)
Renal vascular disease	16 (23.9)	21 (29.6)
Other cause	29 (43.3)	34 (47.9)
Diabetes mellitus, n (%)	20 (29.9)	15 (21.1)
Cardiovascular disease, n (%) [b]	24 (35.8)	28 (39.4)
Kidney transplant recipient, n (%) [c]	17 (25.4)	10 (14.1)
Sodium excretion rate, mean ± SD, mmol/24-hour [d]	151.1 ± 66.9	176.1 ± 60.9
Sodium-to-creatinine ratio, mean ± SD, mmol/g (24-hour) [e]	103.7 ± 44.4	114.7 ± 40.9
Protein excretion rate, median (IQR), g/24-hour [f]	0.70 (0.33-1.33)	0.91 (0.41-2.16)
eGFR, mean ± SD, mL/min/1.73 m^2 [g]	47.6 ± 25.0	51.8 ± 26.2
BSA-corrected CLcr, median (IQR), mL/min/1.73 m^2 [h]	46.0 (32.3-69.3)	55.1 (40.1-81.8)
Potassium excretion rate, mean ± SD, mmol/24-hour [i]	69.8 ± 21.5	73.5 ± 28.1
Haemoglobin, mean ± SD, g/dL [j]	14.1 ± 1.9	13.7 ± 1.5
Total cholesterol, mean ± SD, mg/dL [l]	197.2 ± 42.5	193.3 ± 38.7
24-hour SBP, mean ± SD, mm Hg [k,m]	129 ±15	128 ±15
24-hour DBP, mean ± SD, mm Hg [k,m]	77 ± 10	75 ± 9
Office SBP, mean ± SD, mm Hg	142 ±19	137 ± 17
Office DBP, mean ± SD, mm Hg	87 ± 11	83 ± 10
Body weight, mean ± SD, kg	90.9 ± 15.7	92.7 ± 16.9
Body mass index, mean ± SD, kg/m^2	29.7 ± 5.4	29.7 ± 5.2
Psychosocial		
Physical HRQOL, mean ± SD [n]	70.8 ± 21.1	65.2 ± 24.3
Mental HRQOL, mean ± SD, [o]	73.9 ± 19.5	72.0 ± 18.1
Self-efficacy mean ± SD [p]	7.5 ± 1.3	7.9 ± 0.9
Medication		
Anti-HTN medication use, n (%)	64 (95.5)	70 (98.6)
Sum score anti-HTN medication, mean ± SD	2.3 (1.2)	2.4 (1.1)
RAAS blockade use, n (%)	50 (74.6)	60 (84.5)
ARBs	27 (40.3)	27 (38.0)
ACE Inhibitors	27 (40.3)	37 (52.1)
Calcium channel blocker use, n (%)	26 (38.8)	29 (40.8)
Beta-blocker use , n (%)	28 (41.8)	30 (42.3)
Diuretics use, n (%)	30 (44.8)	35 (49.3)
A1-Adrenergic blocker use, n (%)	8 (11.9)	3 (4.2)
Other anti-HTN medication use, n (%)	8 (11.9)	2 (2.8)

Note: Values for categorical variables are given as count (proportion); values for continuous variables are given as mean ± standard deviation for normally distributed variables or median [boundaries of interquartile range] for skewed variables. Conversion factor for cholesterol in mg/dL to mmol/L, x 0.02586. Low education was classified as: primary education and lower secondary education. Abbreviations: ACE, angiotensin-converting enzyme; ABPM, ambulatory blood pressure monitoring; ARBs, angiotensin II type 1 receptor antagonists; BSA, body surface area; CLcr, creatinine clearance; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; HTN, hypertension; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure. [a] Primary kidney disease was classified into 4 categories according to European Renal Association/European Dialysis and Transplant Association codes.[50] [b] Cardiovascular disease was defined by the presence of angina pectoris, coronary disease, and/or myocardial infarction. [c] To meet inclusion criteria, transplantation had to have occurred < 1 year prior to inclusion. Complete data available with the exception of the following variables, with data available for: [d] 66 intervention patients (99%) and 66 control patients (93%), [e] 65 intervention patients (97%) and 66 control patients (93%), [f] 63 intervention patients (94%) and 66 control patients (93%), [g] 64 control patients (90.1%), [h] 65 intervention patients (97.0%) and 62 control patients (87.3%), [i] 66 intervention patients (99%) and 65 control patients (92%), [j] 65 control patients (92%), [l] 64 control patients (90%), [m] 58 intervention patients (87%) and 55 control patients (78%), [n] 63 intervention patients (94%) and 70 control patients (99%), [o] 63 intervention patients (94%) and 69 control patients (97%), and [p] 64 intervention patients (96%) and 69 control patients (97%). [k] A total of 133 complete ABPM measurements were available: 66 in the intervention group (99%) and 67 in the control group (94%). Following the guidelines for reliable ABPM measurements, recordings were blind evaluated and 20 ABPM measurements (15%) were excluded from analyses (8 [12%] in the intervention group and 12 [18%] in the control group).

No significant differences between groups were detected in antihypertensive medication, kidney function, and HRQOL. In addition, the intervention group had a reduction in body weight compared to the control group (mean change, -1.5 [95% CI, -2.7 to -0.3] kg).

At 6 months

No significant differences in sodium excretion and ambulatory BP measurements were found at the 6-month follow-up, but several other differences were observed (see Table 2). Compared to regular care only, the intervention resulted in -7.3 (95% CI, -12.7 to -1.9) and -3.8 (95% CI, -6.9 to -0.6) mm Hg mean changes in systolic and diastolic office BPs, respectively, and a mean change of -0.3 (95% CI, -0.6 to -0.1) g/24-hour in protein excretion rate. There was a 0.5 (95% CI, 0.0 to 0.9) mean increase in self-efficacy score in the intervention group compared to the control group.

No significant differences between groups were detected in antihypertensive medication, kidney function, and HRQOL. In addition, there was a reduction in body weight in the intervention group compared to the control group (mean change, -1.7 [95% CI, -2.9 to -0.5] kg).

All within- and between-group effects are shown in Table 2, Figure 2 (sodium excretion, protein excretion, and systolic and diastolic 24-hour BPs), and Figure S1 (all other outcomes). Finally, sensitivity analysis showed that most results remained stable, including the analysis adjusted for baseline covariates, the analysis without adjustments, and as-treated analysis (see Item S2).

Discussion

To our knowledge, ESMO is the first study to investigate whether sodium intake in patients with CKD can be changed by means of a theory-based self-management intervention and to evaluate not only the effectiveness, but also the sustainability of this real-life intervention. Results indicate that compared to regular care only, this behavioural approach can modestly decrease risk factors for disease progression in patients with CKD. However, effects on the primary outcomes – sodium excretion and ambulatory BP – following the intervention diminish over time.

The findings of this study are partly in agreement with previous research. In contrast to the MASTERPLAN study,[20] but in accordance with the study of de Brito-Ashurst et al.,[19] we found that sodium intake in patients with CKD can be modified by means of a self-management intervention. Compared to the intervention effect of de Brito-Ashurst et al.[19] of 103 mmol/24-hour, our reduction of 30 mmol could be considered modest. Compared to the Trials of Hypertension Prevention (TOHP) II study, which evaluated a multifactorial sodium intervention in overweight nonhypertensive adults and found sodium reductions of 44 and 38 mmol/24-hour,[40] our sodium reduction could be considered similar but was not maintained for 6 months. Possible explanations for the discrepancies can be found in the intervention design. First, our intervention was a low intensity intervention compared to the 3-year TOHP II intervention comprising more than 15 contact moments.[40,41]

Table 2. Intention to treat analysis adjusted for the baseline value (N = 138)

	Mean (standard error of the mean)						Effect intervention (95% CI)	
	Intervention group			Control group				
	T0	T1	T2	T0	T1	T2	Δ T0 - T1	Δ T0 - T2
Sodium								
Sodium excretion, mmol/24-hour	159.4 (6.0)	138.3 (6.5)*	157.0 (6.4)	167.7 (6.0)	176.9 (6.6)	162.5 (6.8)	-30.3 (-54.7 to -5.9)†	2.9 (-21.6 to 27.3)
Blood pressure								
24-hour SBP, mm Hg	129 (1.1)	125 (1.2)*	128 (1.2)	128 (1.1)	127 (1.2)	130 (1.2)	-2.2 (-6.4 to 1.9)	-2.1 (-6.3 to 2.1)
24-hour DBP, mm Hg	76 (0.7)	74 (0.8)*	75 (0.8)	76 (0.7)	76 (0.8)	77 (0.8)	-2.4 (-5.1 to 0.3)	-2.2 (-4.9 to 0.5)
Day SBP, mm Hg	132 (1.1)	128 (1.3)**	131 (1.3)	132 (1.2)	131 (1.3)	133 (1.3)	-2.9 (-7.2 to 1.4)	-1.9 (-6.3 to 2.4)
Day DBP, mm Hg	80 (0.7)	77 (0.8)**	78 (0.8)	79 (0.8)	80 (0.9)	80 (0.9)	-3.4 (-6.3 to -0.6)†	-2.3 (-5.2 to 0.5)
Night SBP, mm Hg	120 (1.2)	117 (1.4)	120 (1.4)	120 (1.3)	120 (1.4)	121 (1.4)	-2.5 (-7.3 to 2.2)	-1.8 (-6.6 to 3.0)
Night DBP, mm Hg	69 (0.8)	68 (0.9)	69 (0.9)	69 (0.9)	69 (0.9)	70 (1.0)	-0.9 (-4.0 to 2.2)	-1.2 (-4.3 to 1.9)
Office SBP, mm Hg	140 (1.5)	134 (1.5)**	133 (1.6)**	138 (1.4)	135 (1.6)	139 (1.6)	-2.9 (-8.3 to 2.4)	-7.3 (-12.7 to -1.9)††
Office DBP, mm Hg	85 (0.9)	80 (0.9)**	81 (0.9)**	84 (0.8)	84 (0.9)	83 (0.9)	-5.2 (-8.4 to -2.1)††	-3.8 (-6.9 to -0.6)†
Clinical								
Protein excretion, g/24-hour	1.2 (0.1)	1.0 (0.1)	1.1 (0.1)	1.2 (0.1)	1.4 (0.2)*	1.4 (0.1)*	-0.4 (-0.7 to -0.1)††	-0.3 (-0.6 to -0.1)†
eGFR, mL/min/1.73 m^2	49.9 (1.1)	49.4 (1.1)	49.6 (1.1)	49.5 (1.1)	49.3 (1.2)	46.9 (1.2)**	-0.3 (-2.9 to 2.3)	2.3 (-0.4 to 4.9)
BSA-corrected CLcr, mL/min/1.73 m^2	59.0 (2.2)	60.7 (2.3)	58.8 (2.3)	59.0 (2.2)	62.8 (2.4)	59.8 (2.4)	-2.2 (-9.8 to 5.4)	-1.0 (-8.7 to 6.7)
Total no. of anti-HTN medications	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)	-0.0 (-0.3 to 0.2)	-0.0 (-0.3 to 0.2)
Body weight, kg	91.4 (0.3)	89.9 (0.4)**	89.8 (0.4)**	91.4 (0.3)	91.4 (0.4)	91.5 (0.4)	-1.5 (-2.7 to -0.3)†	-1.7 (-2.9 to -0.5)††
Psychosocial								
Physical HRQOL	68.9 (1.7)	69.3 (1.8)	65.4 (1.8)	67.5 (1.6)	65.4 (1.8)	66.4 (1.9)	2.4 (-3.3 to 8.2)	-2.4 (-8.2 to 3.3)
Mental HRQOL	73.7 (1.5)	75.8 (1.6)	75.2 (1.6)	72.9 (1.4)	72.7 (1.6)	74.9 (1.7)	2.3 (-3.1 to 7.7)	-0.5 (-5.9 to 4.9)
Self-efficacy	7.6 (0.1)	8.1 (0.1)**	7.9 (0.1)	7.8 (0.1)	7.8 (0.1)	7.6 (0.1)	0.5 (0.1 to 0.9)†	0.5 (0.0 to 0.9)†

Abbreviations: BSA, body surface area; CI, confidence interval; CLcr, creatinine clearance; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; HTN, hypertension; SBP, systolic blood pressure; T0, baseline; T1, 3 months' follow-up; T2, 6 months' follow-up. * $P < 0.05$, ** $P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. † $P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

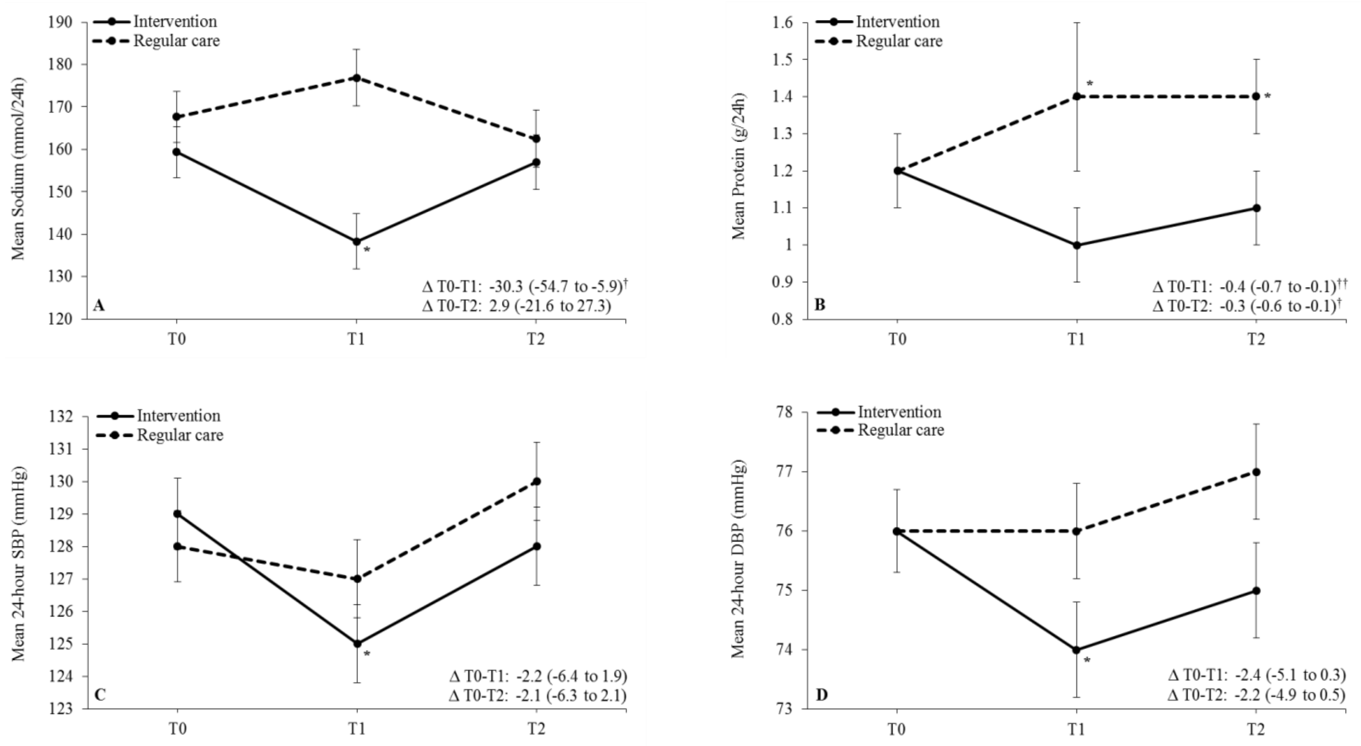

Figure 2. Within- and between-group effects of primary intention-to-treat analyses adjusted for baseline value: (A) sodium excretion, (B) protein excretion, (C) 24-hour systolic blood pressure (SBP), and (D) 24-hour diastolic blood pressure (DBP). Abbreviations: T0, baseline; T1, 3 months' follow-up; T2, 6 months' follow-up. * $P < 0.05$, ** $P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. † $P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

Although evidence for intensity as a moderator for effectiveness of lifestyle interventions is inconclusive (e.g., Greaves et al.[11] found intensity to be a moderator, but Janssen et al.[42] did not), increased intervention intensity might have resulted in maintaining the low-sodium diet. Second, our intervention could be regarded as an individual-oriented intervention compared to the de Brito-Ashurst et al.[19] and TOHP II[40] interventions, which comprised group meetings. Planning social support was part of our intervention and significant others were invited to attend meetings. However, only 23 (34%) patients brought significant others, and social support among fellow patients was not facilitated. Given that social support is associated with lifestyle adherence,[11,43] increased social support might have led to stronger effects. Third, the intervention of de Brito-Ashurst et al.[19] included cooking lessons, whereas ESMO participants received a kidney-friendly cookbook. Perhaps including low-sodium cooking sessions instead of merely providing written instructions could have resulted in larger sodium reductions. Finally, the TOHP II intervention included an extended phase using follow-up prompts.[41] In our study, contact frequency was gradually reduced, but follow-up prompts (e.g., postcards or booster sessions) were not included. Follow-up prompts have been associated with increased effectivity[10]; therefore, including an extended phase could have resulted in maintaining the low-sodium diet.

Similar to the literature,[3,16,17,19] our sodium intervention also reduced BP. However, our ambulatory BP reductions did not remain significant at the 6-month follow-up time and could be considered modest compared to the 8/2 mm Hg reduction in 24-hour BP by the self-management intervention of de Brito-Ashurst et al.[19] and the reduction of 9/4 mm Hg (combining 24-hour and office measures) found by a recent meta-analysis.[3] Discrepancies could be explained by study design (i.e., the meta-analysis included many crossover studies and effectiveness was only measured directly after interventions) and the larger sodium intervention effects of approximately 100 mmol/24-hour found in these studies.[3,19]

In accordance with previous crossover studies,[14-17] results showed that our intervention reduced protein excretion, but our effects (reductions of 0.4 and 0.3 g/24-hour at 3 and 6 months) seem small compared to the reduction of 0.8 g/24-hour found by Vogt et al.,[15] for example. However, the baseline protein excretion rate in our group was low compared to that in Vogt et al. (i.e., 1.2 versus 3.8 g/24-hour), and hence the percentage decrease in protein excretion could be considered comparable. Furthermore, the literature suggests that reducing sodium intake could have beneficial effects on CKD progression.[12,13] However, our study was underpowered to detect differences in kidney function and our follow-up was too short to confirm long-term beneficial effects. In line with this, no significant group differences were detected, although estimated glomerular filtration rates decreased in the control group.

In accordance with the literature,[24] this intervention also increased patients' beliefs that they are capable of managing their kidney disease. However, contrary to Campbell et al.,[23] our intervention did not improve HRQOL. This discrepancy might be explained by patient characteristics; whereas Campbell et al. included non-dialysis-dependent patients with advanced CKD with impaired HRQOL, we included patients with moderately decreased kidney function and relatively high HRQOL.

Finally, although not specified in the original protocol, a reduction in body weight was also observed in the intervention group. This finding corresponds partially with the literature; previous studies found decreased body weight after sodium interventions,[15,36] but significant body weight reductions have not been found in the study by de Brito-Ashurst et al.[19] and a recent meta-analysis.[3] An explanation for our intervention effect could be that the weight reduction was not sodium specific, but due to weight loss goals that 21 (31%) participants set in addition to sodium goals. Unfortunately, objective markers of body composition were not collected to attribute this reduced body weight to either changes in body fat or fluid status.

Specific strengths of this study include a tailored intervention according to the needs of patients and health care professionals as assessed in a preparatory qualitative study[5] and the application of multiple evidence-based behaviour change techniques.[7-11] Furthermore, because self-monitoring is a component of effective lifestyle interventions[9,42] and patients with CKD have stressed the need for additional feedback regarding sodium,[5] the inclusion of two sodium self-monitoring tools (i.e., online diary and sodium measurement device) could be seen as a strength. However, patients also encountered problems with these self-monitoring tools, which might have hampered the effectiveness of this intervention (e.g., negative feelings or less feedback on sodium intake). Therefore, the inclusion of these self-monitoring tools could also be considered a study limitation. Another limitation is nonblinding; due to the active nature of the intervention, concealment of randomization was not possible. In addition, it is possible that trial participation and active recruitment caused both groups to reduce their sodium intakes prior to baseline measurements. This potential Hawthorne effect[44] might have contributed to the modest effects found. Furthermore, this study has missing data that could possibly lead to biases. However, because clinical trials often deal with missing data, we performed intention-to-treat analyses to avoid overestimating intervention effects.[45] To avoid biased estimates and loss of power, we also used linear mixed modelling and performed analyses while adjusting for imputed missing baseline values (1.7% in the intervention group and 3.8% in the control group).[39] Our response rate could also be considered relatively low and hence limits generalization of results. However, similar response rates have been found in previous self-management interventions (e.g., 47% by Bucknall et al.[46]). Finally, we included a heterogeneous group including patients who might have different renal responses to sodium restriction. However, recent studies have shown that sodium restriction also effectively reduced BP in patients who had received transplants[47] and in patients with type 2 diabetic nephropathy.[48] Moreover, inclusion of different patient groups could be considered a strength as well because patients under nephrologic care represent a highly heterogeneous group, and hence increases the generalizability of our results.

With this study, we report a small but important step to support patients with CKD in reducing sodium intake. However, additional research is needed to provide further insight into the intervention effects, for instance, the change in (amounts of) high- or low-sodium food products by means of food diary data. Furthermore, given that self-efficacy is associated with self-care behaviours,[43,49] additional research is needed to investigate the mediating role of self-efficacy. Finally, future studies should also investigate whether the ESMO intervention effects could be improved by including a more robust and user-friendly sodium measurement device and a less complex online food diary, intensifying the intervention, involving patients' social environment, and adding booster sessions.

Conclusions

In conclusion, compared to regular care alone, this theory-based sodium self-management intervention modestly improved risk factors for disease progression in patients with CKD, although effects on sodium and ambulatory BP following the intervention diminished over time.

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Supplementary materials

Chapter 4

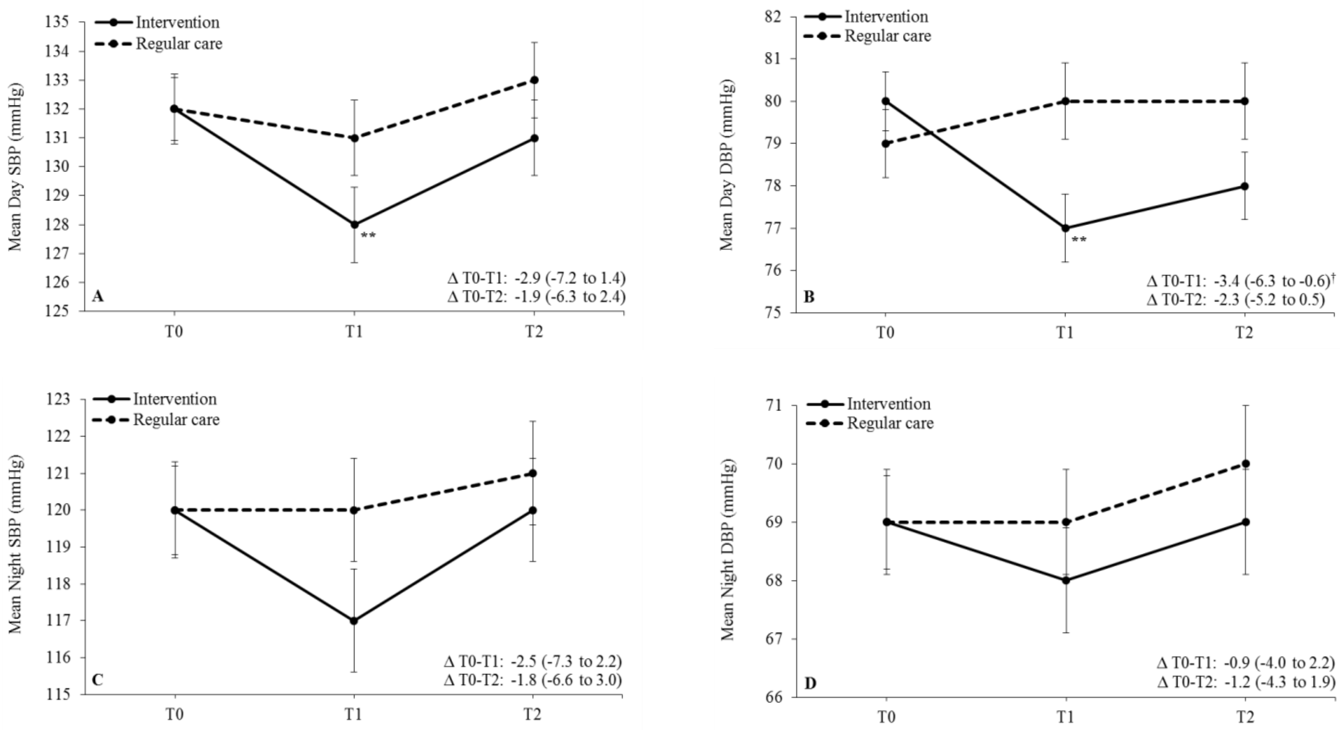

Figure S1. Within and between group effects of the primary intention to treat analyses adjusted for the baseline value: daytime systolic blood pressure (A), daytime diastolic blood pressure (B), nighttime systolic blood pressure (C) and nighttime diastolic blood pressure (D). Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; T0, baseline; T1, 3 months' follow-up; T2, 6 months' follow-up. * $P < 0.05$, $^{**}P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. $^{\dagger}P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

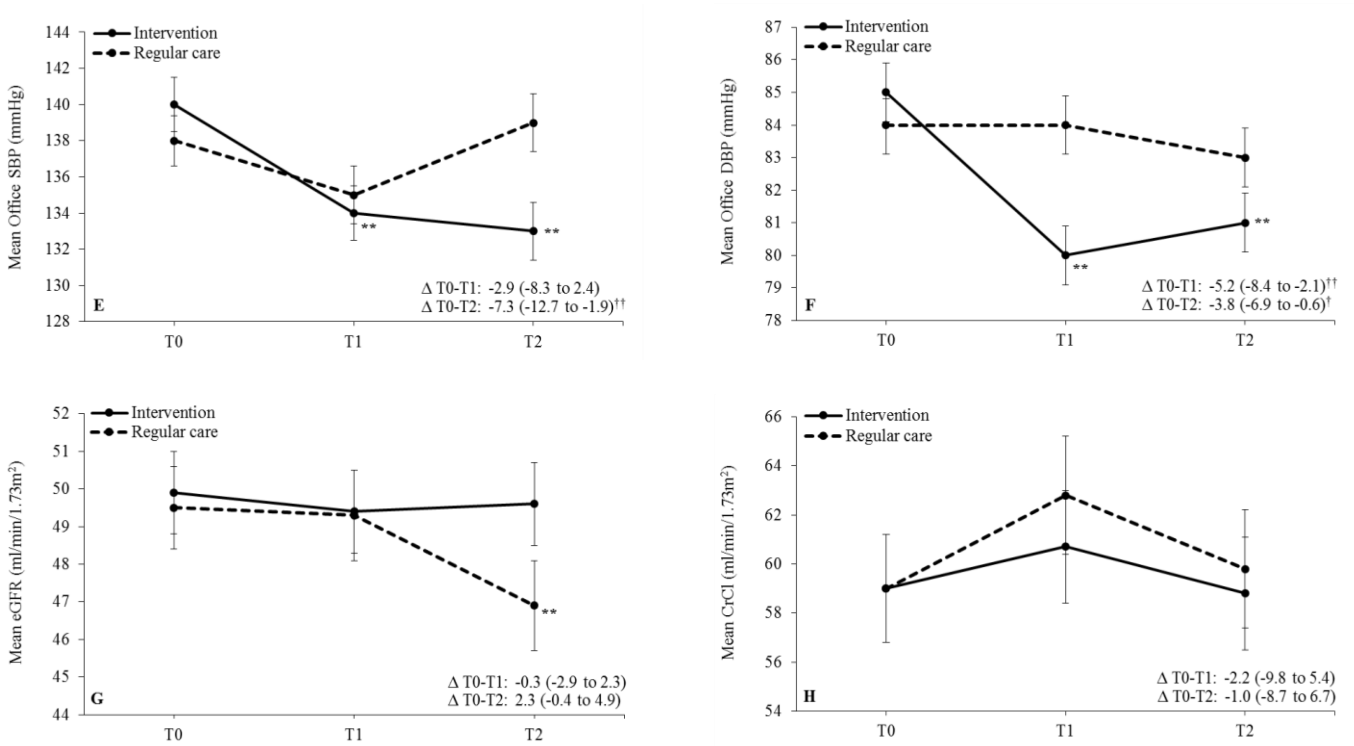

Figure S1. Within and between group effects of the primary intention to treat analyses adjusted for the baseline value: systolic office blood pressure (E), diastolic office blood pressure (F), estimated glomerular filtration rate (G) and creatinine clearance (H). Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; CrCl, Creatinine clearance; T0, baseline; T1, 3 months' follow-up; T2, 6 months' follow-up.* $P < 0.05$, ** $P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. † $P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

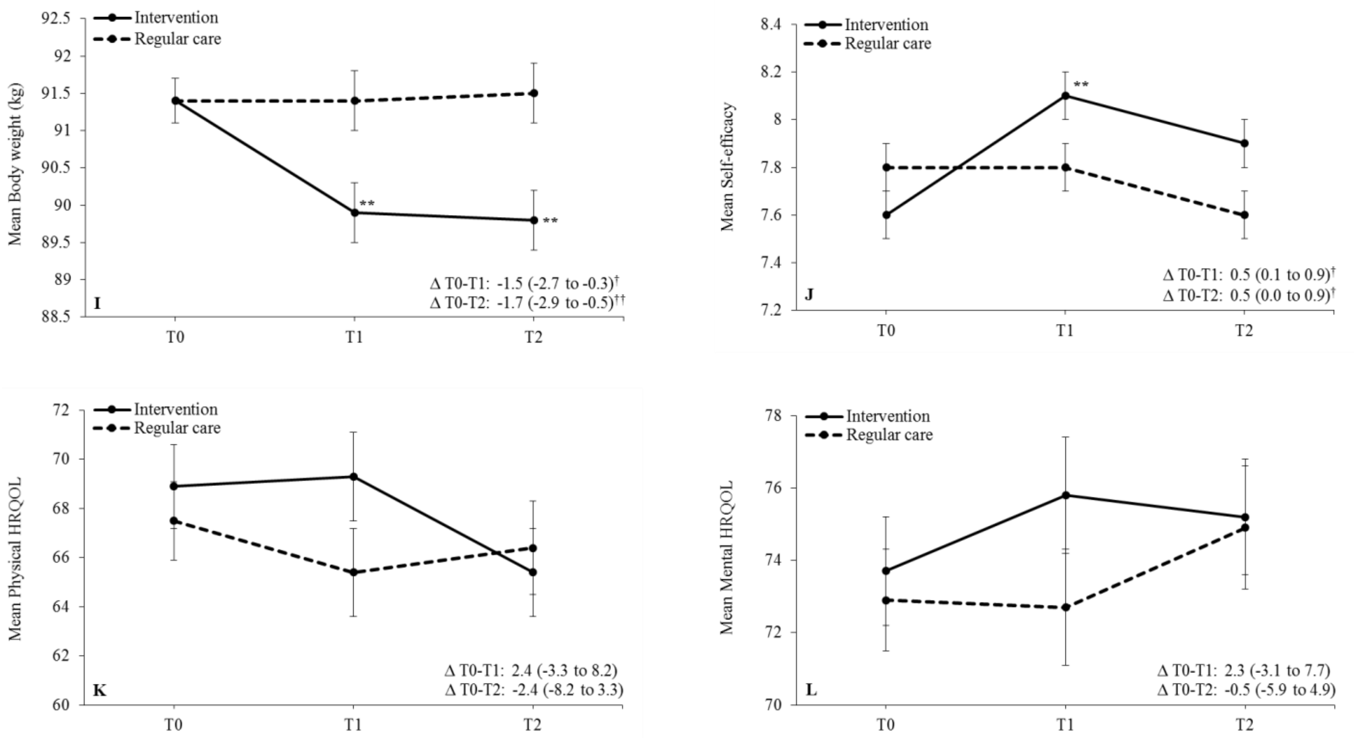

Figure S1. Within and between group effects of the primary intention to treat analyses adjusted for the baseline value: body weight (I), self-efficacy (J), physical health-related quality of life (K) and mental health-related quality of life (L). Abbreviations: HRQOL, health-related quality of life; T0, baseline; T1, 3 months' follow-up; T2, 6 months' follow-up. $^{*}P < 0.05$, $^{**}P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

Item S1: Content and fidelity of the intervention based on the CALO-RE Taxonomy

To assure the fidelity of the intervention, all coaches followed the intervention protocol regarding the required frequency and content of the contact moments in the intervention. In the instructions, coaches were informed about which subjects should be addressed during these contact moments and which techniques should be used to address these subjects. For detailed information on the content of and behaviour change techniques used during the intervention, please see Supplementary Table S1 below.

Supplementary Table S1: Content of the intervention based on the CALO-RE Taxonomy

	Week		
Behaviour change techniques (number of the technique)	**1**	**2 - 11**	**12**
Motivational interviewing (37)	x		x
Provide information on consequences (1,2)	x		
Provide normative information about others' behaviour (4)	x		
Prompting focus on past success (18)	x		
Goal setting – behaviour and outcome (5,6)	x		
Agree behavioural contract (25)	x		
Action planning (7)	x	x	
Barrier identification/problem solving (8)	x	x	
Set graded tasks (9)	x	x	
Plan social support/social change (29)	x	x	
Provide instruction on how to perform the behaviour (21)	x	x	
Environmental restructuring (24)		x	
Prompt practice (26)		x	
Prompt generalisation of target behaviour (15)		x	
Prompt self-monitoring of behaviour and outcome (16,17)		x	x
Prompt review of behavioural goals and outcome goals (10,11)		x	x
Provide feedback on performance (19)		x	x
Provide rewards contingent on successful behaviour (13)		x	x
Relapse prevention/coping planning (35)			x

Note: Reporting the content of this intervention according to the standardized method of CALO-RE Taxonomy, strengthen the knowledge about active ingredients of interventions, and increases the possibility of replicating interventions and synthesizing evidence.[1]

1. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. *Psychol Health*. 2011;26:1479-98.

Item S2: Sensitivity analyses

Methods

Several sensitivity analyses were performed to test the robustness of our results. All sensitivity analyses were conducted using linear mixed modelling. All models included the following fixed variables: group, time, and the various continuous dependent variables. An interaction term was also included as fixed variable: group * time, which indicated the effect (i.e., change in scores on dependent variables) of the study group by time. Furthermore, the models included patient-level random effects to account for correlation between patients' repeated measures over time. First, the primary intention to treat analyses were repeated with baseline covariates to adjust for potential imbalances in baseline characteristics of the groups (Model 2). The following differences between the groups were taken into account: compared to the control group, patients in the intervention group were more often female, did not have a Dutch nationality, were higher educated, and were more often married or cohabiting. Moreover, they had more often diabetes mellitus, received a kidney transplantation, a higher systolic and diastolic office blood pressure, a lower kidney function, and lower self-efficacy. When data of baseline covariates were missing, data was imputed using multiple imputation (using 10 repetitions). Second, the primary intention to treat analyses were repeated without adjustments (Model 3). Third, as-treated analyses were conducted with non-compliant intervention patients treated as control group (Model 4). Fourth, to investigate trial effects due to active recruitment, the primary intention to treat analysis was repeated with sodium excretion measures prior to baseline (median [IQR] of 2 [1 - 3] months before baseline measures). Fifth, to correct for possible collection errors and body size, the primary intention to treat analysis was repeated with sodium and protein excretion normalized to urinary creatinine excretion (i.e., calculating the sodium-to-creatinine and protein-to-creatinine ratio) while adjusting for the baseline value. Finally, the primary intention to treat analysis was repeated with the blood pressure related factor 24-hour potassium excretion while adjusting for the baseline value.

Abbreviations: BSA, body surface area; CI, confidence interval; CLcr, creatinine clearance; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; HTN, hypertension; SBP, systolic blood pressure; T0, baseline; T1, 3 months' follow-up; T2, 6 months' follow-up.

Table A. Model 2: Intention to treat analysis adjusted for baseline covariates (N = 138) [a]

	Mean (standard error of the mean)						Effect intervention (95% CI)	
	Intervention group			Control group				
	T0	T1	T2	T0	T1	T2	Δ T0 - T1	Δ T0 - T2
Sodium								
Sodium excretion, mmol/24-hour	159.3 (8.6)	138.1 (9.0)*	156.8 (8.9)	166.5 (8.9)	174.5 (9.6)	160.4 (9.4)	-29.2 (-53.7 to -4.7)†	3.6 (-20.9 to 28.2)
Blood pressure								
24-hour SBP, mm Hg	132 (3.1)	129 (3.2)	131 (3.2)	133 (3.3)	132 (3.3)	135 (3.3)	-2.1 (-6.4 to 2.2)	-1.9 (-6.3 to 2.6)
24-hour DBP, mm Hg	78 (1.8)	75 (1.9)*	76 (1.9)	77 (1.9)	77 (2.0)	78 (2.0)	-2.2 (-5.0 to 0.6)	-2.1 (-4.5 to 0.2)
Day SBP, mm Hg	135 (3.0)	131 (3.0)*	134 (3.1)	136 (3.1)	135 (3.2)	137 (3.2)	-2.6 (-4.9 to 0.3)	-1.9 (-4.2 to 0.5)
Day DBP, mm Hg	81 (1.8)	78 (1.9)**	80 (1.9)	80 (1.9)	81 (2.0)	81 (2.0)	-3.2 (-6.2 to -0.2)†	-2.2 (-5.2 to 0.7)
Night SBP, mm Hg	122 (3.7)	121 (3.7)	123 (3.7)	127 (3.9)	126 (3.9)	128 (3.9)	-1.4 (-6.4 to 3.5)	-0.7 (-5.2 to 3.7)
Night DBP, mm Hg	69 (2.0)	68 (2.1)	69 (2.1)	71 (2.1)	71 (2.2)	72 (2.2)	-0.0 (-3.1 to 3.0)	-0.4 (-3.5 to 2.7)
Office SBP, mm Hg	141 (2.3)	135 (2.3)**	134 (2.3)**	140 (2.3)	137 (2.5)	140 (2.4)	-3.2 (-8.5 to 2.2)	-7.5 (-12.9 to -2.1)††
Office DBP, mm Hg	86 (1.3)	81 (1.3)**	81 (1.3)**	84 (1.3)	85 (1.4)	83 (1.4)	-5.3 (-8.5 to -2.2)††	-3.8 (-7.0 to -0.6)†
Clinical								
Protein excretion, g/24-hour	1.0 (0.3)	0.8 (0.3)*	0.9 (0.3)	1.3 (0.3)	1.5 (0.3)*	1.5 (0.3)*	-0.4 (-0.7 to -0.2)††	-0.4 (-0.7 to -0.1)††
Body weight, kg	86.3 (3.3)	84.8 (3.3)**	84.8 (3.3)**	87.6 (3.4)	87.6 (3.4)	87.7 (3.4)	-1.5 (-2.2 to -0.9)†	-1.7 (-2.3 to -1.1)††
eGFR, mL/min/1.73 m^2	49.2 (2.2)	48.6 (2.2)	48.8 (2.2)	48.5 (2.1)	48.3 (2.2)	46.0 (2.1)**	-0.4 (-3.0 to 2.2)	2.2 (-0.5 to 4.8)
BSA-corrected CLcr, mL/min/1.73 m^2	60.2 (3.8)	61.6 (3.9)	59.4 (3.9)	61.1 (3.9)	64.0 (4.2)	60.8 (4.0)	-1.5 (-9.3 to 6.4)	-0.5 (-8.5 to 7.4)
Psychosocial								
Physical HRQOL	66.1 (4.7)	66.0 (4.8)	62.4 (4.8)	57.2 (4.8)	55.5 (4.9)	56.3 (4.9)	1.6 (-4.3 to 7.5)	-2.7 (-8.6 to 3.2)
Mental HRQOL	72.3 (3.8)	74.3 (3.9)	73.8 (3.9)	68.6 (3.9)	68.8 (4.0)	70.6 (4.0)	1.7 (-3.7 to 7.2)	-0.5 (-6.0 to 5.0)
Self-efficacy	7.7 (0.2)	8.2 (0.2)**	8.0 (0.2)	8.0 (0.2)	8.0 (0.2)	7.8 (0.2)	0.5 (0.1 to 1.0)†	0.5 (0.0 to 0.9)†

[a] Adjusted for baseline covariates: gender, ethnicity, marital status, education, diabetes mellitus, kidney transplantation, sodium excretion, kidney function, systolic and diastolic office blood pressure, and self-efficacy. * $P < 0.05$, ** $P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. † $P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

Table B. Model 3: Intention to treat analysis crude (N = 138)

	Mean (standard error of the mean)						Effect intervention (95% CI)	
	Intervention group			Control group				
	T0	**T1**	**T2**	**T0**	**T1**	**T2**	**Δ T0 - T1**	**Δ T0 - T2**
Sodium								
Sodium excretion, mmol/24-hour	151.3 (7.8)	129.1 (8.4)*	149.5 (8.3)	175.0 (7.8)	184.9 (8.5)	173.5 (8.6)	-32.1 (-57.5 to -6.8)†	-0.3 (-25.8 to 25.1)
Blood pressure								
24-hour SBP, mm Hg	129 (1.9)	126 (2.0)*	129 (2.0)	127 (1.9)	126 (2.0)	129 (2.0)	-2.3 (-6.7 to 2.1)	-2.2 (-6.6 to 2.2)
24-hour DBP, mm Hg	77 (1.2)	75 (1.3)*	76 (1.3)	75 (1.2)	75 (1.3)	76 (1.3)	-2.5 (-5.4 to 0.3)	-2.5 (-5.4 to 0.3)
Day SBP, mm Hg	133 (1.8)	129 (1.9)*	132 (1.9)	131 (1.9)	130 (2.0)	133 (2.0)	-2.7 (-7.3 to 1.9)	-2.1 (-6.7 to 2.5)
Day DBP, mm Hg	80 (1.2)	77 (1.3)**	79 (1.3)	78 (1.3)	79 (1.3)	79 (1.3)	-3.5 (-6.5 to -0.6)†	-2.5 (-5.5 to 0.4)
Night SBP, mm Hg	120 (2.2)	118 (2.3)	121 (2.3)	120 (2.2)	120 (2.3)	121 (2.3)	-1.9 (-6.9 to 3.0)	-1.3 (-6.4 to 3.7)
Night DBP, mm Hg	69 (1.3)	69 (1.4)	70 (1.4)	69 (1.3)	68 (1.4)	70 (1.4)	-0.5 (-3.7 to 2.7)	-0.9 (-4.1 to 2.3)
Office SBP, mm Hg	142 (2.1)	136 (2.2)**	135 (2.2)**	137 (2.1)	134 (2.2)	137 (2.3)	-3.1 (-8.7 to 2.5)	-7.3 (-13.0 to -1.7)†
Office DBP, mm Hg	87 (1.3)	82 (1.3)**	82 (1.3)**	83 (1.2)	83 (1.3)	82 (1.4)	-5.4 (-8.7 to -2.1)††	-4.0 (-7.3 to -0.7)†
Clinical								
Protein excretion, g/24-hour	1.1 (0.2)	0.9 (0.2)	1.0 (0.2)	1.3 (0.2)	1.6 (0.2)*	1.6 (0.2)*	-0.4 (-0.7 to -0.1)††	-0.4 (-0.6 to -0.1)†
Body weight, kg	90.9 (2.0)	89.4 (2.0)**	89.4 (2.0)**	92.7 (1.9)	92.7 (2.0)	92.9 (2.0)	-1.5 (-2.7 to -0.3)†	-1.7 (-2.9 to -0.5)††
eGFR, mL/min/1.73 m^2	47.6 (3.1)	47.1 (3.1)	47.3 (3.1)	51.0 (3.1)	50.9 (3.1)	48.8 (3.1)*	-0.5 (-3.0 to 2.1)	1.9 (-0.7 to 4.5)
BSA-corrected CLcr, mL/min/1.73 m^2	55.4 (4.3)	57.4 (4.4)	55.6 (4.4)	61.3 (4.3)	65.5 (4.5)	63.0 (4.5)	-2.1 (-10.1 to 5.8)	-1.4 (-9.5 to 6.6)
Psychosocial								
Physical HRQOL	70.9 (2.8)	70.9 (2.9)	67.3 (2.9)	64.8 (2.7)	63.1 (2.9)	63.8 (2.9)	1.7 (-4.2 to 7.6)	-2.6 (-8.5 to 3.3)
Mental HRQOL	74.7 (2.4)	76.5 (2.5)	76.0 (2.5)	71.5 (2.4)	71.6 (2.5)	73.4 (2.5)	1.6 (-3.9 to 7.1)	-0.7 (-6.2 to 4.9)
Self-efficacy	7.5 (0.1)	8.0 (0.1)**	7.8 (0.1)	7.9 (0.1)	7.9 (0.1)	7.7 (0.1)	0.5 (0.1 to 1.0)†	0.5 (0.0 to 0.9)†

* $P < 0.05$, ** $P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. † $P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

Table C. Model 4: As-treated analysis (N = 138) [a]

	Mean (standard error of the mean)						Effect intervention (95% CI)	
	Intervention group			Control group				
	T0	T1	T2	T0	T1	T2	Δ T0 - T1	Δ T0 - T2
Sodium								
Sodium excretion, mmol/24-hour	159.6 (6.6)	137.5 (6.7)*	158.8 (6.6)	166.3 (5.5)	175.7 (6.5)	160.4 (6.6)	-31.5 (-56.1 to -7.0)†	5.1 (-19.6 to 29.7)
Blood pressure								
24-hour SBP, mm Hg	129 (1.2)	125 (1.2)*	128 (1.2)	128 (1.0)	128 (1.2)	129 (1.2)	-3.2 (-7.3 to 1.0)	-1.4 (-5.6 to 2.7)
24-hour DBP, mm Hg	76 (0.8)	74 (0.8)**	75 (0.8)	76 (0.7)	76 (0.8)	77 (0.8)	-2.7 (-5.4 to -0.0)†	-1.7 (-4.4 to 1.0)
Day SBP, mm Hg	132 (1.2)	128 (1.3)**	131 (1.3)	132 (1.1)	131 (1.3)	133 (1.3)	-3.6 (-7.9 to 0.7)	-1.0 (-5.4 to 3.3)
Day DBP, mm Hg	80 (0.8)	76 (0.9)**	79 (0.9)	79 (0.7)	80 (0.8)	80 (0.9)	-3.7 (-6.6 to -0.9)††	-1.7 (-4.6 to 1.1)
Night SBP, mm Hg	120 (1.4)	117 (1.4)	119 (1.4)	120 (1.2)	121 (1.4)	121 (1.4)	-3.6 (-8.4 to 1.2)	-1.6 (-6.5 to 3.2)
Night DBP, mm Hg	69 (0.9)	68 (1.0)	69 (1.0)	69 (0.8)	69 (0.9)	70 (0.9)	-1.1 (-4.2 to 1.9)	-1.0 (-4.1 to 2.1)
Office SBP, mm Hg	139 (1.6)	133 (1.6)**	132 (1.6)**	139 (1.3)	136 (1.5)	139 (1.6)	-3.2 (-8.6 to 2.2)	-6.9 (-12.3 to -1.5)†
Office DBP, mm Hg	85 (0.9)	80 (0.9)**	81 (0.9)**	84 (0.8)	84 (0.9)	83 (0.9)	-5.1 (-6.8 to -3.5)††	-2.8 (-6.0 to 0.4)
Clinical								
Protein excretion, g/24-hour	1.2 (0.1)	1.1 (0.1)	1.1 (0.1)	1.2 (0.1)	1.4 (0.1)	1.4 (0.1)	-0.3 (-0.6 to -0.0)†	-0.2 (-0.5 to 0.0)
Body weight, kg	91.4 (0.4)	89.7 (0.4)**	89.8 (0.4)**	91.4 (0.3)	91.4 (0.4)	91.5 (0.4)	-1.7 (-2.9 to -0.4)††	-1.7 (-2.9 to -0.5)††
eGFR, mL/min/1.73 m^2	50.0 (1.2)	49.1 (1.2)	49.5 (1.2)	49.5 (1.0)	49.6 (1.1)	47.1 (1.1)*	-1.0 (-3.6 to 1.6)	1.8 (-0.9 to 4.5)
BSA-corrected CLcr, mL/min/1.73 m^2	59.2 (2.4)	60.1 (2.4)	57.8 (2.4)	58.8 (2.0)	63.3 (2.4)	60.7 (2.4)	-3.6 (-11.3 to 4.0)	-3.3 (-11.0 to 4.4)
Psychosocial								
Physical HRQOL	69.1 (1.8)	69.6 (1.9)	65.4 (1.9)	67.6 (1.5)	65.4 (1.8)	66.5 (1.8)	2.7 (-3.1 to 8.5)	-2.5 (-8.3 to 3.3)
Mental HRQOL	73.9 (1.7)	76.0 (1.7)	75.2 (1.7)	72.9 (1.3)	72.8 (1.6)	74.9 (1.6)	2.3 (-3.2 to 7.7)	-0.7 (-6.2 to 4.7)
Self-efficacy	7.6 (0.1)	8.1 (0.1)**	7.9 (0.1)	7.8 (0.1)	7.7 (0.1)	7.6 (0.1)	0.6 (0.1 to 1.0)†	0.5 (0.0 to 0.9)†

[a] Intervention group include compliant intervention participants (n = 55), and control group additionally include non-compliant intervention participants (n = 83).
* $P < 0.05$, ** $P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. † $P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from group with control and non-compliant intervention participants.

Table D. Intention to treat analysis sodium prior to baseline, sodium- and protein-to-creatinine ratio, and potassium excretion

	Mean (standard error of the mean)						Effect intervention (95% CI)	
	Intervention group			Control group				
	T0	T1	T2	T0	T1	T2	Δ T0 - T1	Δ T0 - T2
Sodium excretion, mmol/24-hour [a]	183.8 (6.3)	132.3 (6.9)**	155.3 (6.8)**	190.9 (6.2)	179.3 (7.0)	167.4 (7.1)*	-39.9 (-65.4 to -14.4)††	-5.0 (-30.5 to 20.6)
Creatinine excretion (g/24-hour)	1.5 (0.1)	1.5 (0.1)	1.5 (0.1)	1.6 (0.1)	1.6 (0.1)	1.7 (0.1)	-0.1 (-0.2 to 0.1)	-0.1 (-0.3 to 0.0)
Sodium-to-creatinine ratio, mmol/g (24-hour)	106.9 (4.3)	94.7 (4.6)*	109.4 (4.6)	111.4 (4.3)	111.0 (4.7)	105.7 (4.8)	-11.8 (-28.9 to 5.3)	8.3 (-8.8 to 25.5)
Protein-to-creatinine ratio, g/g (24-hour)	0.8 (0.1)	0.7 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	-0.2 (-0.4 to -0.0)†	-0.1 (-0.3 to 0.1)
Potassium excretion (mmol/24-hour)	71.9 (2.4)	74.0 (2.7)	71.1 (2.7)	72.4 (2.4)	77.0 (2.8)	78.3 (2.8)	-2.4 (-11.5 to 6.7)	-6.7 (-15.8 to 2.3)

[a] T0 = median (IQR) of 2 (1 - 3) months prior to baseline, T1 = three months follow-up and T2 = six months follow-up. * $P < 0.05$, ** $P < 0.01$ – mean (standard error of the mean) differs significantly from baseline. † $P < 0.05$, †† $P < 0.01$ – change in mean over time (95% confidence interval) differs significantly from control group.

Conclusions

When repeating the analysis while adjusting for baseline covariates (Model 2; see Table A), without adjustments (Model 3; see Table B), and as-treated analysis (Model 4; see Table C), the results did not change essentially with the exception that in Model 4 now a significant group difference in 24-hour diastolic ambulant blood pressure was detected at three months (-2.7; 95% CI, -5.4 to -0.0 mm Hg), but the group differences in diastolic office blood pressure and protein excretion at six months were not significant anymore.

Furthermore, at the median (IQR) of 2 (1 - 3) months prior to baseline, patients in both groups had a higher sodium excretion compared to baseline measures (mean [SD] was 178.3 [54.7] mmol/24-hour in the intervention group and 195.6 [67.8] mmol/24-hour in the control group). Repeating the analysis using sodium excretion at median (IQR) 2 (1 - 3) months before the trial as baseline measure, resulted in a larger reduction in the intervention group at three months (-51.5; 95% CI, -69.4 to -33.5 mmol/24-hour), and now a significant sodium reduction was found at six months (-28.5; 95% CI, -46.4 to -10.6 mmol/24-hour). Moreover, a significant sodium reduction was now also found in the control condition at six months (-23.5; 95% CI, -41.8 to -5.3 mmol/24-hour), however, the results regarding the group differences did not change essentially (see Table D).

Repeating the analysis with sodium-to-creatinine ratio and protein-to-creatinine ratio did not change the results essentially with the exception that no significant group difference in sodium-to-creatinine ratio was found at three months, and no significant group difference in protein-to-creatinine ratio was detected at six months (see Table D). Finally, no significant changes of potassium excretion in both groups were observed (see Table D).

Chapter 5

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

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Abstract

Background

In predialysis patients, the optimal treatment choices for controlling haemoglobin (Hb) are unknown, because targeting high Hb levels has negative effects – poorer survival – but possible positive effects as well – better health-related quality of life (HRQOL). Moreover, these effects may be different in specific subgroups (e.g., young versus elderly).

Methods

In the PREPARE-2 follow-up study, incident predialysis patients were included (2004 - 2011) when referred to 1 of the 25 participating Dutch outpatient clinics. HRQOL was assessed at 6-month intervals with the 36-item Short Form Health Survey [physical/mental summary measure and eight subscales (range 0 - 100)]. A linear mixed model was used to associate Hb [< 11, ≥ 11 to < 12 (reference), ≥ 12 to < 13, and ≥ 13 g/dL] with HRQOL, stratified by prescription of anaemia medication (erythropoietin-stimulating agent [ESA]/iron) and age (young: < 65 years and elderly: ≥ 65 years).

Results

Only elderly patients (n = 214) not prescribed ESA/iron and with a high Hb (≥ 13 versus ≥ 11 to < 12 g/dL) had a statistically significant ($P < 0.05$) and/or clinically relevant (> 3 - 5 points) higher physical (11.9; 95% confidence interval [CI], 1.7 to 22.2) and mental (6.4; 95% CI, -1.7 to 14.6) summary score. High Hb was not associated with a higher HRQOL in elderly patients who were prescribed ESA/iron. However, only young patients (n = 157) prescribed ESA/iron and with a high Hb (≥ 13 versus ≥ 11 to < 12 g/dL) had a higher physical (8.9; 95% CI, 2.1 to 15.8) and mental (6.2; 95% CI, -0.4 to 12.8) summary score.

Conclusions

The association of Hb levels with HRQOL differs by age and use of ESA/iron medication on predialysis care. Therefore, medical care should aim for shared decision-making regarding the appropriate Hb target leading to more individualized care.

Introduction

Anaemia is a common complication in patients with chronic kidney disease (CKD),[1] and is associated with increased mortality and morbidity, lower health-related quality of life (HRQOL) and faster progression to end-stage kidney disease.[2-9] Therefore, treatment of anaemia with an erythropoietin stimulating agent (ESA), iron supplements or a combination of the two is important, and several studies have shown that treatment with ESA has a beneficial effect on various health outcomes.[10-14]

However, the optimal haemoglobin (Hb) treatment target level for anaemic patients with CKD is still unknown. A meta-analysis[15] showed that targeting high Hb levels (≥ 12 g/dL) with ESA in anaemic CKD patients increases their HRQOL. Positive effects were predominantly found on the physical summary measure of the 36-item Short Form Health Survey (SF-36).[16] These effects are biologically plausible, because common symptoms like low energy, fatigue and weakness can be ameliorated by treating anaemic patients with ESA.[11] Moreover, increasing HRQOL may have additional positive effects independently of other factors, because it has been shown that starting dialysis with a high HRQOL increases survival.[17,18] Besides the positive effects on HRQOL, high Hb targets (≥ 12 g/dL) in CKD patients can also have negative effects, such as an increased risk of mortality and cardiovascular events, and an accelerated progression to end-stage kidney disease.[19] These contradictory results on different health outcomes indicate that it is important to make a well-considered treatment decision, taking personal preferences of CKD patients into account. Good clinical practice would be that each patient discusses the possible positive effects on HRQOL and the possible negative effects on other clinical outcomes together with their physician to make an informed decision about the appropriate Hb treatment target.

Unfortunately, there is still insufficient evidence regarding the effect of targeting high Hb levels with anaemia medication on HRQOL to make such a well-considered decision. The studies that are available do not report all HRQOL subscales, do not show clinically relevant effects and only report results about a heterogeneous population, instead of different subgroups of CKD patients. For example, positive effects on HRQOL may vary by age and CKD stage. Elderly patients and late-stage CKD patients experience more morbidities and have a lower HRQOL compared with young[20] and early-stage CKD[21] patients. A lower HRQOL may lead to a larger possible improvement. Or the opposite may take place, in which treatment ameliorates anaemia-related symptoms whereas other morbidity-related symptoms among older patients in late CKD stages remain present, and consequently lead to a less increased HRQOL.

The aim of this study was to gain more knowledge about the combined association of Hb levels and the prescription of anaemia medication with all HRQOL subscales, in elderly compared with young CKD patients starting specialized predialysis care.

Methods

Study design

The PREdialysis PAtient REcord-2 (PREPARE-2) study is an ongoing, prospective follow-up study of incident predialysis patients treated in 25 nephrology outpatient clinics in the Netherlands. Patients were included between July 2004 and June 2011, at the start of specialized predialysis care. They were treated by their nephrologist in their regular scheme according to the treatment guideline of the Dutch Federation of Nephrology,[22] a guideline partly based on the Kidney Disease Outcomes Quality Initiative[23] and Kidney Disease Improving Global Outcomes[24] guidelines. Patients were followed up until the start of dialysis, receiving a kidney transplant, death or censoring. Censoring was defined as moving to an outpatient clinic not participating in the PREPARE-2 study, recovery of kidney function, refusal of further study participation, lost to follow-up or 1 August 2012 (end of follow-up), whichever came first. The study was approved by the medical ethics committee or the institutional review board (as appropriate) of all participating centres.

Patients

To be eligible for inclusion, patients had to be at least 18 years of age and the inclusion should take place at the moment of referral to a specialized predialysis outpatient clinic. In practice, this refers to incident predialysis patients with an estimated glomerular filtration rate (eGFR) of < 20 - 30 mL/min/1.73 m^2, in whom kidney function loss is progressive. Patients with a failing kidney transplant were also included in the study, if the transplantation was at least one year ago. All participants gave their written informed consent prior to study inclusion.

Data collection

Data on demography, biometry, primary kidney disease, comorbidities, medication prescriptions and HRQOL were collected at the start of specialized predialysis care and at subsequent 6-month intervals. Corresponding laboratory data were extracted from the electronic hospital information systems or medical records. Primary kidney disease was classified according to the codes of the European Renal Association - European Dialysis and Transplantation Association.[25]

Measurements and definitions

HRQOL was assessed with the generic validated 36-item Short Form Health Survey,[16] which consists of 36 items that can be divided into 8 subscales. The scores on the items within each subscale are summed and transformed to a 0 - 100 scale, with higher scores indicating a better HRQOL. Two summary measures can be composed of the eight subscales: physical summary score (consisting of the four subscales: physical functioning, role-physical, bodily pain and general health) and mental summary score (consisting of the four subscales: vitality, social functioning, role-emotional and mental health). GFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula.[26] The Hb levels (in mmol/L) were measured according to the standard procedure in each participating outpatient clinic. We converted the Hb level in mmol/L to g/dL with the conversion factor 1.6113 and categorized it into four groups (< 11, ≥ 11 to < 12, ≥ 12 to < 13, and ≥ 13 g/dL). The chosen categories were based on the current treatment guideline for anaemic CKD patients (target is ≥ 11 to < 12 g/dL, and ≥ 13 g/dL should not be targeted[27]).

Statistical analysis

Continuous baseline characteristics were presented as mean ± standard deviation (SD) or median (boundaries of interquartile range [IQR]) and categorical baseline characteristics were presented as percentages. A linear mixed model was used to associate the Hb categories (≥ 11 to < 12 g/dL as reference) with HRQOL during the first 2 years of predialysis care. We chose to restrict the time of follow-up until 2 years to prevent selection bias, as the healthy and stable patients, whom are still on predialysis care after 2 years, would have a relatively large contribution to the overall association. In the model we included the four Hb categories as a fixed independent variable and the continuous HRQOL as a dependent variable, both updated every 6 months, and the variable time as a random variable. The results from this model indicate the difference in HRQOL score between the different Hb categories (compared with the reference category ≥ 11 to < 12 g/dL) on each time point during the first 2 years of predialysis care. In other words, the results indicate the 'average' HRQOL difference between Hb categories. This linear mixed model was also performed after stratification by (i) the prescription of anaemia medication (ESA and/or iron supplement [ESA/iron]) at the start of predialysis care (yes/no) and (ii) age (young: < 65 years and elderly: ≥ 65 years). To avoid power problems, we also performed a continuous (per 1 g/dL increase) analysis in patients with Hb levels ≥ 11 g/dL (i.e., patients with optimal and high Hb levels). Patients with Hb levels < 11 g/dL were excluded, because categorical analyses before stratification showed a different effect size on HRQOL in these patients. We adjusted for the potential baseline confounders age, sex, primary kidney disease, cardiovascular disease, diabetes mellitus, eGFR, proteinuria, albumin and systolic blood pressure. Associations of Hb with HRQOL were interpreted both statistically (*p*-value < 0.05) and clinically (categorical analyses: > 3 - 5 points,[28] and for the continuous analyses: > 1.5 - 2.5 points per 1 g/dL increase). When information on stratification variables – age and ESA/iron prescription – or confounders were missing at the start of predialysis care, data were imputed with the method of multiple imputation in SPSS (using 10 repetitions). Multiple imputation is a technique where missing data for a patient are imputed by a value that is predicted by other known characteristics of this patient.[29,30] The imputation model included all characteristics described in Tables 1 and 2, plus the outcome reached and follow-up time, because missing baseline characteristics are often related to the outcome.[31] Skewed distributed continuous variables, including follow-up time, were logarithmically transformed before entering into the model. All statistical analyses were performed with SPSS version 20.0.

We performed six sensitivity analyses to test the robustness of our results. First, we repeated all analyses after imputation of the missing baseline characteristics of all 502 included patients. Second, after defining young patients as < 70 years and elderly patients as ≥ 70 years, analyses were repeated. Third, we repeated all linear mixed model analyses with an additional interaction term in the model: Hb categories * time. By including this term we investigated whether the association between Hb and HRQOL is different over time. In other words, whether the pattern of HRQOL over time differs between the Hb categories. Fourth, during predialysis care, some patients discontinue and others start using ESA/iron and patients can switch from the category < 65 to ≥ 65 years. Therefore, we included the time-dependent variables ESA/iron prescription and age (young: < 65 years and elderly: ≥ 65 years), updated every 6 months, during predialysis care in the linear mixed model, instead of stratifying the analyses by ESA/iron prescription and age at the start of predialysis care. Fifth, we performed an additional analysis with the potential confounders systolic blood pressure, eGFR, proteinuria and albumin also included as time-dependent variables. Thereafter, we repeated all analyses after excluding patients with a failing kidney transplant at the moment of referral (n = 11).

Results

Baseline characteristics

Of the 502 patients included in the PREPARE-2 study, 371 patients were included in our primary statistical analysis. Patients were excluded if a Hb measurement and physical or mental summary score in the same 6-month interval during the first 2 years of predialysis care were not available. Table 1 shows the baseline clinical characteristics of these patients. Respectively, 19%, 30% and 51% had Hb levels below, on or above the current treatment target (≥ 11 to < 12 g/dL). The majority had renal vascular disease as primary kidney disease and often diabetes mellitus as comorbidity. Patients with Hb levels ≥ 13 g/dL had a higher eGFR, lower body mass index, less often diabetes mellitus and more often cardiovascular disease compared with patients on target (≥ 11 to < 12 g/dL). Moreover, the higher prevalence of cardiovascular disease was mainly present in elderly patients (≥ 65 years; 62% for ≥ 13 g/dL and 45% for ≥ 11 to < 12 g/dL) and not in young patients (< 65 years; 32 and 28%, respectively). Information regarding prescription of medication at the start of predialysis care was available only for 323 (87%) patients (see Table 2). Of these, 54% were prescribed ESA/iron therapy, which was similar across all Hb levels. Darbepoetin and iron supplements (orally administered in the majority of patients) were prescribed more often than epoetin (30% versus 18%), especially in patients with high Hb levels (≥ 12 g/dL). The median ESA dose was 4000 units/week in patients on target (≥ 11 to < 12 g/dL) and in patients with Hb levels below or above this target.

Table 1. Baseline clinical characteristics of the total study population and stratified by categories of Hb levels (g/dL)

	Total N = 371	<11[a] n = 68	≥11 to <12[a] n = 104	≥12 to <13[a] n = 75	≥13[a] n = 106
Age, years, mean ± SD	69 (55-76)	70 (51-78)	69 (57-75)	69 (57-76)	65 (53-76)
Sex, male, n (%)	248 (67)	41 (60)	70 (67)	49 (65)	77 (73)
BMI, kg/m2, mean ± SD [b]	26.4 ± 4.9	27.0 ± 5.4	26.3 ± 5.0	26.4 ± 4.6	26.1 ± 4.8
Smokers/quitters <1 year before inclusion, n (%)	90 (24)	12 (18)	25 (24)	18 (24)	29 (27)
Primary kidney disease, n (%)					
Diabetes mellitus	49 (13)	12 (18)	11 (11)	9 (12)	14 (13)
Glomerulonephritis	52 (14)	7 (10)	15 (14)	13 (17)	13 (12)
Renal vascular disease	112 (30)	28 (41)	29 (28)	22 (29)	31 (29)
Other	158 (43)	21 (31)	49 (47)	31 (42)	48 (46)
eGFR, mL/min/1.73 m^2, mean ± SD [c]	16.9 ± 6.0	15.5 ± 4.9	15.9 ± 5.9	17.6 ± 5.2	18.4 ± 6.8
Protein excretion, g/24-hour, median (IQR) [d]	1.0 (0.3-2.1)	1.1 (0.3-2.0)	1.0 (0.4-2.4)	0.7 (0.2-2.0)	1.1 (0.4-2.2)
Urea, mmol/L, mean ± SD [e]	22.1 ± 7.0	23.7 ± 7.1	22.6 ± 6.9	21.1 ± 6.4	21.4 ± 7.5
Albumin, g/L, mean ± SD [f]	40.7 ± 4.6	39.1 ± 5.0	40.5 ± 4.4	41.3 ± 4.7	41.5 ± 4.5
Systolic blood pressure, mm Hg, mean ± SD [g]	142 ± 22	142 ± 23	144 ± 24	139 ± 19	141 ± 23
Hb, g/dL, mean ± SD, [a]	12.3 ± 1.5	10.3 ± 0.5	11.6 ± 0.3	12.5 ± 0.3	14.0 ± 0.9
C-reactive protein, mg/L, median (IQR) [h]	4.8 (2.3-8.1)	7.0 (3.3-18.3)	3.0 (2.0-6.8)	5.0 (3.0-8.8)	5.0 (1.1-6.0)
Diabetes mellitus, n (%) [i]	96 (26)	26 (38)	26 (25)	16 (21)	23 (22)
Cardiovascular disease, n (%) [j]	158 (43)	27 (40)	40 (39)	31 (41)	50 (47)

Continuous variables are presented as mean ± SD for normally distributed variables and as median (IQR) for skewed variables. [a] Hb level is available for 353 patients, [b] BMI is available for 366 patients, [c] GFR is estimated with the MDRD formula and available for 351 patients, [d] Urinary protein excretion is available for 210 patients, [e] Urea is available for 338 patients, [f] Albumin is available for 324 patients, [g] Systolic blood pressure is available for 368 patients, [h] C-reactive protein is available for 170 patients. [i] Present as primary kidney disease or comorbidity. [j] Defined as the presence of a cerebrovascular accident, vascular problems, angina pectoris, myocardial infarction or decompensation cordis.

Table 2. Baseline treatment characteristics of the total study population and stratified by categories of Hb levels (g/dL)

	Total N = 323	<11[a] n = 60	≥11 to <12[a] n = 90	≥12 to <13[a] n = 66	≥13[a] n = 92
ESA, n (%)	154 (48)	31 (52)	42 (47)	37 (56)	39 (42)
Dose, units/week [b]	4000 (2000-6000)	4000 (2250-7500)	4000 (2000-6000)	4000 (2000-6000)	4000 (2000-6462)
Epoetin	57 (18)	14 (23)	19 (21)	11 (17)	12 (13)
Dose, units/week	4000 (2000-5750)	4500 (3000-7000)	3000 (2000-4000)	5000 (3500-8500)	3500 (2000-4000)
Darbepoetin	97 (30)	17 (28)	23 (26)	26 (39)	27 (29)
Dose, units/week	4000 (2000-7192)	4000 (2000-8000)	4000 (2077-7500)	2667 (2000-5600)	4000 (2000-8000)
Iron, n (%)	98 (30)	18 (30)	29 (32)	19 (29)	30 (33)
Oral, n (%)	97 (99)	18 (100)	29 (100)	19 (100)	29 (97)
Intravenous, n (%)	1 (1)	0 (0)	0 (0)	0 (0)	1 (3)
ESA/iron, n (%)	175 (54)	34 (57)	49 (54)	41 (62)	45 (49)

Abbreviations: ESA, erythropoietin-stimulating agent. [a] Hb level is available for 308 patients. [b] Doses are presented as median (IQR) and available for 142 patients.

Association of Hb levels with HRQOL

Patients with high Hb levels (≥ 13 g/dL) had a statistically ($P < 0.05$) and clinically (> 3 - 5 points) higher physical summary score (56.7 versus 51.8, see Table 3) compared with patients on target (≥ 11 to < 12 g/dL). Adjustment for confounders did not essentially change the results. On all physical subscales, with the exception of bodily pain, this difference was clinically relevant. Furthermore, patients with low Hb levels (< 11 g/dL) had a lower mental summary score compared with patients on target (60.4 versus 66.1, $p < 0.05$). On all subscales of the mental summary measure, with the exception of mental health, this difference was clinically relevant.

Table 3. Association of Hb levels (g/dL) with HRQOL on each time point during predialysis care

	<11 Mean (95% CI)	≥11 to <12 Mean (95% CI)	≥12 to <13 Mean (95% CI)	≥13 Mean (95% CI)
Physical summary score	49.9 (46.5-53.2)	*51.8 (48.9-54.8)*	53.9 (50.9-56.9)	56.7 (53.6-59.8) [a,b]
Physical functioning	54.3 (50.6-58.0)	*56.5 (53.1-59.9)*	59.6 (56.3-63.0) [a]	60.7 (57.2-64.2) [a,b]
Role-physical	39.7 (32.9-46.6)	*43.0 (37.1-48.9)*	43.1 (37.2-49.1)	50.3 (44.2-56.4)
Bodily pain	65.1 (61.1-69.2) [a,b]	*70.8 (67.3-74.3)*	71.6 (68.1-75.1)	73.6 (70.0-77.1)
General health	38.5 (35.8-41.1)	*38.7 (36.4-41.0)*	40.0 (37.7-42.3)	41.8 (39.4-44.1) [a,b]
Mental summary score	60.4 (57.2-63.7) [a,b]	*66.1 (63.3-68.9)*	66.4 (63.6-69.3)	67.7 (64.8-70.6)
Vitality	47.9 (44.9-50.9) [a,b]	*52.8 (50.2-55.5)*	52.6 (49.9-55.2)	52.9 (50.2-55.7)
Social functioning	65.3 (61.5-69.1) [a,b]	*73.0 (69.7-76.3)*	71.7 (68.3-75.0)	75.3 (71.9-78.7)
Role-emotional	62.1 (55.4-68.7)	*68.6 (63.1-74.1)*	69.1 (63.4-74.7)	71.9 (66.6-77.2)
Mental health	70.1 (67.3-72.8)	*72.8 (70.4-75.2)*	73.4 (71.0-75.8)	73.5 (71.0-75.9)

For each Hb category the mean score on the two summary measures and eight subscales with its 95% CI is given. The *p*-values are from a linear mixed model investigating whether the scores were significantly different compared with the reference category (Hb level of ≥ 11 to < 12 g/dL, given in italics). [a] Crude p-value < 0.05. [b] Adjusted p-value < 0.05: sex, age, primary kidney disease, eGFR, proteinuria, albumin, systolic blood pressure, cardiovascular disease and diabetes mellitus.

Association of Hb levels with HRQOL, stratified by ESA/iron prescription and age

Young patients (< 65 years) not prescribed ESA/iron at the start of predialysis care had similar physical and mental summary scores across all Hb levels (see Tables 4 and 5). When young patients were prescribed ESA/iron, high Hb levels (≥ 13 g/dL) resulted in a statistically significant and clinically relevant higher physical (8.9; 95% CI, 2.1 to 15.8) and clinically relevant mental summary score (6.2; 95% CI, -0.4 to 12.8) compared with young patients on target (≥ 11 to < 12 g/dL, see Table 4).

Comparable results were found when analysing Hb levels continuously; per 1 g/dL increase of Hb, the physical summary score increased with 4.0 (95% CI, 1.2 to 6.7) and the mental summary score with 2.4 (95% CI, -0.1 to 4.9) points in patients with Hb levels ≥ 11 g/dL (see Table 5). On all physical and mental subscales, with the exception of mental health, this difference was clinically relevant (> 1.5 - 2.5 points increase with each 1 g/dL Hb increase, see Figure 1A and 1B).

Elderly patients (≥ 65 years) not prescribed ESA/iron at the start of predialysis care with high Hb levels (≥ 13 g/dL) had a statistically significant and clinically relevant higher physical and clinically relevant mental summary score compared with elderly patients with Hb levels ≥ 11 and < 12 g/dL (11.9 [95% CI, 1.7 to 22.2] and 6.4 [95% CI, -1.7 to 14.6], respectively, see Table 4). Continuous analyses showed similar results; per 1 g/dL increase of Hb, the physical summary score increases with 3.6 (95% CI, -0.1 to 7.2) and the mental summary score with 2.5 (95% CI, -0.6 to 5.6) points in patients with a Hb level ≥ 11 g/dL (see Table 5). On all physical subscales and the mental subscales role-emotional and mental health, this difference was clinically relevant (see Figure 1C and 1D). In contrast, in elderly patients who were prescribed ESA/iron higher Hb levels were not associated with HRQOL. However, low Hb levels (< 11 g/dL) were associated with a lower physical (-7.4; 95% CI, -13.7 to -1.0) and mental summary score (-14.2; 95% CI, -20.7 to -7.6) compared with target Hb levels (see Table 4). Adjustment for confounders did not essentially change the results (see Table 4).

Sensitivity analysis

Our first sensitivity analysis showed that results were essentially the same when repeating analyses after imputation or after defining young patients as < 70 instead of < 65 years. None of the linear mixed models showed a significant interaction term between Hb categories and time, indicating that the association of Hb with HRQOL did not change during predialysis care. Using time-dependent variables of ESA/iron prescription, age and the potential confounders during predialysis care also did not change the results. Finally, exclusion of the 11 patients with a failing kidney transplant at the moment of referral did not influence our results.

Table 4. Association of categorical Hb levels (g/dL) with the physical and mental summary score on each time point during predialysis care, stratified by ESA/iron prescription and age

	n at baseline	<11, Crude Δ score (95% CI)	≥11 to <12	≥12 to <13, Crude Δ score (95% CI)	≥13, Crude Δ score (95% CI)
Physical summary score					
Young - No ESA/iron	79	-1.1 (-9.4 to 7.1)	Ref	-3.1 (-9.5 to 3.2)	-0.9 (-8.2 to 6.4)
Elderly - No ESA/iron	88	1.5 (-7.0 to 10.1)	Ref	4.1 (-4.4 to 12.6)	11.9 (1.7 to 22.2) [a,b]
Young - ESA/iron	78	1.7 (-6.1 to 9.4)	Ref	2.2 (-4.5 to 8.9)	8.9 (2.1 to 15.8) [a,b]
Elderly - ESA/iron	126	-7.4 (-13.7 to -1.0) [a]	Ref	3.7 (-1.7 to 9.0)	1.1 (-5.0 to 7.2)
Mental summary score					
Young - No ESA/iron	79	1.8 (-6.5 to 10.1)	Ref	0.4 (-6.1 to 6.9)	0.0 (-7.4 to 7.3)
Elderly - No ESA/iron	88	-3.0 (-10.0 to 3.9)	Ref	1.1 (-5.7 to 7.9)	6.4 (-1.7 to 14.6) [b]
Young - ESA/iron	78	-1.5 (-8.5 to 5.6)	Ref	2.7 (-3.7 to 9.2)	6.2 (-0.4 to 12.8)
Elderly - ESA/iron	126	-14.2 (-20.7 to -7.6) [a,b]	Ref	-1.2 (-6.7 to 4.3)	-2.6 (-8.8 to 3.6)

For each Hb category the difference in the physical and mental summary score (Δ score) with its 95% CI is given, compared with the reference category (Hb level of ≥ 11 to < 12 g/dL, given in italics). All analyses were stratified by ESA/iron prescription at the start of predialysis care and age (young: < 65 years and elderly: ≥ 65 years). The *p*-values are from a linear mixed model investigating whether the scores were significantly different between the Hb categories. [a] Crude *p*-value < 0.05. [b] Adjusted *p*-value < 0.05: sex, age, primary kidney disease, eGFR, proteinuria, albumin, systolic blood pressure, cardiovascular disease and diabetes mellitus.

Table 5. Association of continuous Hb levels (g/dL) with the physical and mental summary score on each time point during predialysis care, stratified by ESA/iron prescription and age

	n at baseline	Hb ≥11 g/dL: optimal and high, per 1 g/dL increase, crude Δ score (95% CI)
Physical summary score		
Young - No ESA/iron	79	1.0 (-1.5 to 3.6)
Elderly - No ESA/iron	88	3.6 (-0.1 to 7.2) [b]
Young - ESA/iron	78	4.0 (1.2 to 6.7) [a,b]
Elderly - ESA/iron	126	1.0 (-1.6 to 3.6)
Mental summary score		
Young - No ESA/iron	79	0.9 (-1.7 to 3.4)
Elderly - No ESA/iron	88	2.5 (-0.6 to 5.6) [b]
Young - ESA/iron	78	2.4 (-0.1 to 4.9)
Elderly - ESA/iron	126	-0.4 (-2.8 to 2.0)

For each 1 g/dL increase in Hb level the difference in the physical and mental summary score (Δ score) with its 95% CI is given. All analyses were stratified by ESA/iron prescription at the start of predialysis care and age (young: < 65 year and elderly: ≥ 65 years). The *p*-values are from a linear mixed model investigating whether the scores significantly changed with each 1 g/dL Hb increase. [a] Crude *p*-value < 0.05. [b] Adjusted *p*-value < 0.05: sex, age, primary kidney disease, eGFR, proteinuria, albumin, systolic blood pressure, cardiovascular disease and diabetes mellitus.

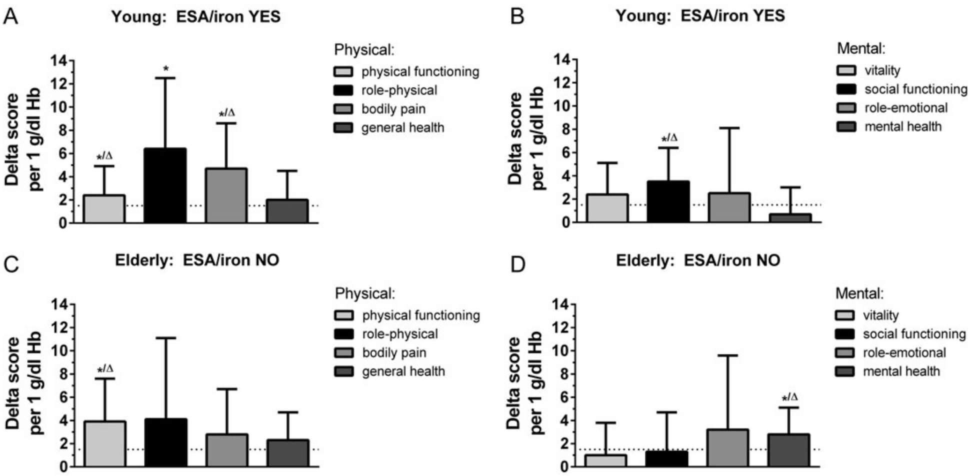

Figure 1. Association of Hb levels with all physical (A and C) and mental (B and D) subscales during predialysis care in patients with Hb levels ≥ 11 g/dL, stratified by ESA/iron prescription and age (young: < 65 years, A and B, and elderly: ≥ 65 years, C and D). The bars indicate the change of the subscale scores (y-axis) and the error bars the 95% CI, with each 1 g/dL Hb increase. Analyses were stratified by ESA/iron prescription at the start of predialysis care and for age (young: < 65 years, and elderly: ≥ 65 years). A linear mixed model was used to investigate the change in subscale scores. The dashed horizontal lines represent an increase in the subscale score of 1.5 - 2.5 points with each 1 g/dL Hb increase, which is considered clinically relevant. Asterisks represent crude p-value < 0.05. Open triangles represent adjusted p-value < 0.05: sex, age, primary kidney disease, eGFR, proteinuria, albumin, systolic blood pressure, cardiovascular disease and diabetes mellitus.

Discussion

This study in patients on specialized predialysis care found several significant improvements in HRQOL throughout different ranges of Hb levels. The most pronounced difference in HRQOL was present in patients with Hb levels on target (≥ 11 to < 12 g/dL) compared with below target and this difference was clinically relevant for the mental summary measure and five subscales; role-physical, bodily pain, vitality, social functioning and role-emotional. In patients with high Hb levels (≥ 13 g/dL), additional increases of HRQOL were present, which were clinically relevant for the physical summary measure and four subscales; physical functioning, role-physical, general health and role-emotional. These findings are in line with the literature, although the study of Finkelstein et al.[3] found a stronger effect on the vitality subscale in the upper Hb ranges.

Although these results in the overall heterogeneous predialysis population are interesting, we should focus on specific subgroups because after stratifying by the prescription of ESA/iron and age (young: < 65 years and elderly: ≥ 65 years), various associations of Hb levels with HRQOL were found. Elderly patients without ESA/iron prescription and with high Hb levels (≥ 13 g/dL) had a clinically relevant higher physical and mental summary score, except on the subscales vitality and social functioning. No association was found in young patients without ESA/iron prescription. Possibly, elderly patients not prescribed ESA/iron and with high Hb levels (≥ 13 g/dL) are very vital (score on the subscale vitality in our data; 51.6) and have less severe comorbidities, and thereby experience a high HRQOL. Furthermore, the absent association of low Hb levels (< 11 g/dL) with HRQOL in both young and elderly patients without ESA/iron prescription may be explained by the presence of clinical indications to not prescribe ESA/iron despite low Hb levels, for instance the absence of anaemia-related symptoms. Another explanation could be the small number of patients with severe anaemia in our study (< 10 g/dL, n = 16).

Besides this, young patients with high Hb levels (≥ 13 g/dL) compared with patients on target (≥ 11 to <12 g/dL) who are prescribed ESA/iron experienced a clinically relevant higher physical and mental summary score, except for the subscale mental health, and this difference was most pronounced for the physical summary measure. In contrast, in elderly patients who are prescribed ESA/iron, no association was found between high Hb levels and better HRQOL. Only elderly patients with low Hb levels (< 11 g/dL) had a lower physical and mental summary score, and this difference was most pronounced on the mental summary measure.

Our finding that in young patients who were prescribed ESA/iron medication, high Hb levels were independently associated with a higher physical summary score is in line with the predialysis trials included in the meta-analysis of Clement et al.[32-36] However, the effects found in these trials were on average smaller than in our study. This discrepancy can be explained by age (our cohort is younger) and a different classification of Hb categories.[32,34,36] Our finding that high Hb levels in young patients who are prescribed ESA/iron were also independently associated with a higher mental summary score is in line with two trials included in the meta-analysis.[32,33] An explanation for finding an increased HRQOL with higher Hb levels in young and not in elderly patients who are prescribed ESA/iron could be the following. Besides anaemia, elderly patients often experience many comorbidities. By prescribing ESA/iron, elderly patients are only relieved of their anaemia-related symptoms and this may lead to a smaller improvement of HRQOL than in young patients. Another explanation could be that, compared with young patients, elderly patients experience less demanding daily activities, such as occupational activities.[37] The effects in young patients were mainly found on the physical subscale role-physical and on the mental subscale social functioning. This finding could be explained by the fact that, generally speaking, daily activities are restored when Hb levels are on target (≥ 11 to < 12 g/dL), but that in young patients a higher Hb level may be necessary to perform all daily activities.

Our study furthermore showed that for 68 patients who were prescribed ESA/iron, Hb levels were still below target (< 11 g/dL). Possible explanations for this low Hb level are ESA resistance (non-responders)[38] and ESA/iron non-compliance. Non-compliance to medication is extremely high (30% - 60%) in patients with chronic illnesses,[39] including patients with CKD.[40] In this study, we found that solely in elderly patients low Hb levels despite ESA/iron prescription were associated with a lower HRQOL, especially regarding the mental summary measure. A possible explanation for this discrepancy could be that elderly patients often have more medications and lifestyle restrictions to be non-compliant to than young patients, due to the presence of multiple comorbidities. Being non-compliant to more than one element of a treatment strategy may lead to suboptimal treatment of multiple comorbidities. This can affect more aspects of health in elderly compared with young patients and can consequently lead to a lower HRQOL. The stronger effect on the mental summary measure could be explained by the fact that normalization of Hb levels with ESA/iron has the strongest effect on the mental subscale vitality[28] and that non-compliance is associated with depressive symptoms and poor well-being.[41,42]

In contrast to the beneficial effect on HRQOL, targeting high Hb levels may have serious disadvantages as well. Consistent with the studies showing a higher risk of cardiovascular events when targeting high Hb levels,[19] we found a higher prevalence of cardiovascular disease in patients with Hb levels ≥ 13 g/dL compared with ≥ 11 to < 12 g/dL (47% versus 39%). Moreover, this higher prevalence of cardiovascular disease was more pronounced in elderly compared with young patients. This finding may implicate that in elderly patients who are prescribed ESA/iron, high Hb levels do lead to negative effects but not give rise to positive effects. This may even more advocate the development of age-specific anaemia treatment guidelines for patients on predialysis care. Unfortunately, we could not investigate whether the mortality risk increases with increasing Hb levels due to the low event rate before the start of dialysis.

A great strength of the PREPARE-2 study is the longitudinal instead of cross-sectional character, resulting in Hb levels and HRQOL measurements for every 6-month interval during predialysis care. Because of these repeated measurements, changes over time, for example HRQOL, can be investigated. Furthermore, our results can be generalized to the complete period of predialysis care in patients with an eGFR < 30 mL/min/1.73 m^2 who are starting specialized predialysis care.

A disadvantage of our study is that we have missing data, because not all patients visited a predialysis outpatient clinic every 6 months and most data was routinely collected. Due to the missing data, we could only include 371 of the 502 patients in our statistical analysis which may lead to selection bias. However, baseline characteristics were similar between the 371 included and 131 excluded patients. Furthermore, results remained similar after imputing missing values at the start of predialysis care for all 502 patients included in the study, which makes it less likely that our analysis suffered from selection bias. However, the exclusion of 131 patients due to missing data did lead to a smaller sample size, and eventually resulted in diminished statistical power after stratification by ESA/iron therapy and age. Another disadvantage is that we stratified by ESA/iron therapy solely based on the prescription of these medications at the start of predialysis care. In practice, the prescription of ESA/iron can change over time. However, results did not change when the prescription of these medications was updated over time. Furthermore, we only know whether ESA/iron was prescribed and we do not know what the medication compliance rates are.

Conclusions

Although trials are needed to confirm our findings, our results indicate that targeting high Hb levels in young, and not in elderly, patients on specialized predialysis care increases their HRQOL. Furthermore, more studies are needed to investigate whether the negative effects of targeting high Hb levels on clinical outcomes are more present in elderly compared with young patients. We believe that future research should investigate negative (mortality and morbidity) and positive (better HRQOL and survival on dialysis) effects in subgroups of specific patients. In addition, future research should also investigate the clinical effect of recent changes in anaemia treatment strategies (including changed targets and ESA doses). This scientific evidence is needed to better inform physicians and patients for making an individualized treatment decision regarding the appropriate Hb target, based on patients' preferences.

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Chapter 6

Health-related quality of life trajectories during predialysis care and associated illness perceptions

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Abstract

Objective

To identify health-related quality of life (HRQOL) trajectories during 18 months of predialysis care and associated patient characteristics and illness perceptions.

Methods

396 incident predialysis patients participating in the prospective PREdialysis PAtient REcord-2 (PREPARE-2) study completed every 6 months the 36-item Short Form Health Survey (i.e., mental and physical HRQOL) and Revised Illness Perception Questionnaire. HRQOL trajectories were examined using latent class growth models, and associated baseline factors were identified using logistic regression. Analyses for illness perceptions were adjusted for demographic and clinical characteristics.

Results

Three physical HRQOL trajectories (low-stable [34.1% of the sample], medium-declining [32.5%], and high-increasing [33.4%]) and two mental HRQOL trajectories (low-stable [38.7%] and high-stable [61.3%]) were identified. Increased odds for a low-stable physical HRQOL trajectory were detected in older patients (Odds Ratio [OR] = 1.04), patients with cardiovascular disease (OR = 2.1) and patients who believed to a lesser extent they can personally control their disease (Odds Ratio adjusted [OR_{adj}] = 0.88). Increased odds for both a low-stable physical and mental HRQOL trajectory were detected in patients who believed to a higher extent that their disease is cyclical, has negative consequences, causes negative feelings, and in patients who believed to a lesser extent they understand their disease (OR_{adj} ranged between 0.84 and 1.36). Additionally, patients who attributed more symptoms to their disease had increased odds for a medium-declining (OR_{adj} = 1.21) and low-stable physical HRQOL trajectory (OR_{adj} = 1.50).

Conclusions

Older age and cardiovascular disease are markers for unfavourable physical HRQOL trajectories, and stronger negative illness perceptions are markers for unfavourable physical and mental HRQOL trajectories. Targeting negative illness perceptions could possibly optimize HRQOL during predialysis care.

Introduction

Individuals with chronic kidney disease (CKD) suffer from a gradual and irreversible loss of kidney function. For most patients, this deterioration in kidney function is accompanied by an increase in symptoms, lifestyle restrictions, and dependency on complex treatment regimens. Consequently, this disease imposes a heavy burden on people's lives, and has a disruptive impact on their health, ability to work, emotional well-being, and social participation.[1]

An important indication of how a disease affects the physical, psychological, and social aspects of patients' lives, is their rating of health-related quality of life (HRQOL). In patients with end-stage kidney disease (ESKD), HRQOL is severely impaired.[2] However, a compromised HRQOL is also evidenced in patients with moderately reduced kidney function and in patients receiving predialysis care (i.e., CKD stages 3 to 5),[3-5] and lower levels of HRQOL in these earlier stages of CKD have been associated with accelerated progression toward ESKD and mortality.[5,6] Therefore, predialysis care not only aims to maximize disease control, but optimizing HRQOL is considered an important treatment goal as well.[7]

Unfortunately, literature regarding HRQOL in patients receiving predialysis care is dominated by cross-sectional studies, and the longitudinal studies that have been conducted found contradictory results regarding the course of HRQOL; some studies found that mean levels of both physical and mental HRQOL decreased over time,[5,8,9] other studies only found changes in one specific physical or mental HRQOL domain (e.g., increased mental health,[10] increased social functioning,[11] and decreased physical function[12]), and there are also studies that found no change in physical or mental HRQOL over time.[13,14] These contradictory results might be due to differences in study design or patient characteristics, but it is also possible that examining mean levels of HRQOL over time masks individual variation in the course of HRQOL. Individuals may differ to a large extent in how their HRQOL develops over time, and the identification of distinct HRQOL trajectories and associated factors could enable personalized treatment approaches in predialysis care. However, to the best of our knowledge, no studies have been conducted that identify HRQOL trajectories during predialysis care using optimal statistical methods such as latent class growth modeling[15] and identified factors associated with these trajectories.

Evidently, previous studies do not provide evidence about factors associated with distinct HRQOL trajectories during predialysis care, but they do point out potentially important factors, including age, gender, kidney function, comorbidities, body mass index (BMI), and levels of albumin and haemoglobin.[3,4,8,11,13,16] Additionally, literature suggests that patients' cognitive appraisal of illness might play a key role in understanding HRQOL: according to the Common Sense Model of self-regulation,[17,18] illness perceptions affect how patients respond to and cope with a health threat, and subsequently contribute to health outcomes. Indeed, studies in patients with CKD show that stronger negative perceptions of illness are associated with various health outcomes, including depressive symptoms,[19] faster disease progression,[20] mortality,[21,22] and impaired HRQOL.[23-27] However, until now, the relationship between illness perceptions and HRQOL has only been investigated in patients with ESKD and information about the longitudinal association is scarce. Examining associations between illness perceptions and HRQOL trajectories during predialysis care could allow the identification of unhelpful illness perceptions and create opportunities to improve HRQOL in earlier stages of CKD.

Therefore, the aim of this study was to examine whether distinct physical and mental HRQOL trajectories during predialysis care could be detected, and to examine if these trajectories are associated with illness perceptions (eight domains: illness identity, timeline acute/chronic, timeline cyclical, negative consequences, personal control, treatment control, illness coherence, and emotional response), demographic (age and gender) and clinical (BMI, comorbidities, kidney function, time since CKD diagnosis, and levels of albumin and haemoglobin) characteristics. It was hypothesized that distinct HRQOL trajectories would be observed and that the factors would differ across the identified trajectories. Due to lacking or inconsistent evidence, no directional a priori hypotheses were formulated.

Methods

Study design

The PREdialysis PAtient REcord-2 (PREPARE-2) study is a prospective follow-up study in 25 specialized nephrology outpatient clinics in the Netherlands. Between July 2004 and June 2011, patients were included at the moment of referral to one of the participating clinics, where they received regular treatment by a multidisciplinary team (consisting of a nephrologist, a nurse practitioner, a dietician, and a social worker) according to the Dutch Federation of Nephrology treatment guidelines[28] (guidelines that are partly based on the Kidney Disease Outcomes Quality Initiative[29] and Kidney Disease Improving Global Outcomes[30] guidelines). Patients were followed until initiation of dialysis, kidney transplantation, a recovered kidney function, transferal to nonparticipating centres, refusal of further participation, death, lost during follow-up, or the end of follow-up (May 13, 2015). Approval by the Medical Ethics Committee or Institutional Review Board of all participating centres was obtained.[a]

Patients

Incident predialysis patients (i.e., within the previous 6 months referred to a specialized predialysis outpatient clinic) with progressive kidney failure and an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 (i.e., CKD stages 4 and 5), were eligible for inclusion, if they were at least 18 years of age. Patients with a kidney transplant dysfunction were also included, if patients received a donor kidney transplant at least one year ago. Prior to study inclusion, written informed consent was obtained from all participants.

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[a] Participating centres: Academic Medical Centre (Amsterdam), Sint Lucas-Andreas Hospital (Amsterdam), VU Medical Centre (Amsterdam), Gelre Hospitals (Apeldoorn), Amphia Hospital (Breda), Reinier de Graaf (Delft), Jeroen Bosch Hospital (Den Bosch), Medical Centre Haaglanden (The Hague), Hospital Gelderse Vallei (Ede), Catharina Hospital (Eindhoven), Scheper Hospital (Emmen), Dialysis Clinic North (Beilen), Admiraal de Ruyter Hospital (Goes), Groene Hart Hospital (Gouda), University Medical Centre Groningen (Groningen), Kennemer Gasthuis (Haarlem), Medical Center Leeuwarden (Leeuwarden), Leiden University Medical Centre (Leiden), Rijnland Hospital (Leiderdorp), Laurentius Hospital (Roermond), Franciscus Hospital (Roosendaal), Franciscus Gasthuis (Rotterdam), Máxima Medical Centre (Veldhoven), Zaans Medical Centre (Zaandam), and Isala Clinics (Zwolle).

Data, definitions, and measurements

Demographic and clinical data were collected during routine visits at the clinics: at the start of predialysis care, at every subsequent 6-month interval, and at the end of follow-up. All clinical measurements were collected according to the standard care of each clinic, and laboratory measurement were periodically extracted from medical records and electronic hospital information systems. As indicator for kidney function, eGFR was calculated by using the abbreviated Modification of Diet in Renal Disease formula.[31] Based on information from medical records, comorbidities were classified as follows: diabetes mellitus (DM; type 1 or 2), and cardiovascular disease (CVD; myocardial infarction, coronary disease, and/or angina pectoris). Patients were also asked to fill out a questionnaire at home, and return the questionnaire as soon as possible. The questionnaire included the 36-item Short Form Health Survey (SF-36) to assess HRQOL.[32] The SF-36 items were divided into two summary scores: a physical composite score (consisting of four subscales: physical functioning, physical role functioning, bodily pain and general health) and a mental composite score (consisting of four subscales: vitality, social role functioning, emotional role functioning, and mental health). Scores were transformed to a 0 - 100 score, with higher scores indicating better HRQOL. The SF-36 showed good reliability with Cronbach alpha values of 0.90 and 0.81 for the physical composite score and mental composite score respectively. The questionnaire also contained the Revised Illness Perception Questionnaire to assess illness perceptions.[33] Seven domains were derived from 38 items scored on a 5-point Likert scale ranging from 1 'strongly disagree' to 5 'strongly agree': timeline acute/chronic, timeline cyclical, negative consequences, personal control, treatment control, illness coherence, and emotional response. The eighth domain, illness identity, was assessed using a sum-score of 14 items in a yes or no format. Like other studies (e.g., Kim & Evangelista[34]), illness perception cause was excluded from the analysis due to heterogeneous causes of CKD. Higher scores on domains reflect that patients attribute more physical symptoms to their kidney disease (i.e., illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e., illness coherence). All domains showed moderate to good reliability with Cronbach alpha values ranging from 0.63 to 0.90 (see Meuleman et al.).[20]

Statistical analysis

To describe patients' baseline characteristics, descriptive statistics were computed. Continuous variables are presented as mean (standard deviation [SD]) for normally distributed variables and as median (boundaries of interquartile range [IQR]) for skewed variables. Chi-square tests of association and t-tests were conducted to investigate if patients who were included in and excluded from analysis differ with regard to baseline characteristics.

To identify distinct groups of patients that share similar HRQOL trajectories during predialysis care, latent class growth models (LCGM) were used. LCGM is a model based cluster analysis approach in order to determine whether longitudinal changes in an outcome may be best described by a single or multiple distinct trajectories (i.e., classes; see also Nagin & Odgers[15]). Four time points were included in the analysis (i.e., baseline, and follow-up measurements at 6, 12, and 18 months) to ensure the availability of sufficient HRQOL measurements and fit the models adequately (i.e., LCGM needs at least three time points to fit the models). As suggested by literature,[35,36] we determined the optimal number of latent trajectory classes by using a combination of several standard fit indices: substantial number of participants in each class (at least 5% of the sample), Bayesian Information Criterion (i.e., lower values indicate a better fit), entropy summary measures (i.e., entropy values range from zero to one, with values closer to one indicating a better quality of the classification), and Vuong-Lo-Mendell-Rubin likelihood test for K-1 versus K classes (i.e., a *p*-value less than 0.05 indicates that the current model has a better fit than the model with one class less). Linear and nonlinear models were evaluated, but in all cases, linear models provided a better fit to the data. To assess the adequacy of the final models, the average posterior probabilities were calculated (i.e., a value of at least 0.70 suggests a good probability that participants belong to the assigned class – there is homogeneity within the class). Labels were assigned to each identified class according to the corresponding class characteristics: the intercept (i.e., the baseline score, for instance: low, medium or high), and the magnitude and direction of the slope (i.e., a statistically significant positive or negative change over time, or the absence of a statistically significant change over time [i.e., a stable trajectory]; see Results).

A series of univariate logistic regression analyses were run to investigate the association between the separate baseline factors (age, gender, eGFR, BMI, DM, CVD, time since CKD diagnosis, serum albumin, haemoglobin, and illness perceptions) and

HRQOL class membership (for details see Jung & Wickrama[35]). Analyses for illness perceptions were repeated using multinomial logistic regression analysis to adjust for age, eGFR, and comorbidities (DM and CVD). For both physical and mental HRQOL models, the reference category was the class representing the highest level of HRQOL (see Results), and effects are expressed as Odds Ratios (ORs) with 95% confidence intervals (CI). Descriptive statistics, Chi-square tests of association and t-tests were conducted using SPSS version 24.0 (IBM). LCGM and logistic regression analyses were run in Mplus version 7.3, and all models used full-information maximum likelihood estimation to addressing missing data (i.e., using all available data under the assumption that data are missing at random) to ensure maximum power and avoided bias estimates.[35,37] *P*-values of < 0.05 were considered statistically significant.

Results

Of the 502 included patients, 396 patients (78.9%) completed the baseline SF-36 (the physical component was completed by 384 patients and the mental component by 394 patients) and were included in the analysis. No significant differences in baseline characteristics (i.e., illness perceptions, demographic and clinical factors; see Table 1) were observed between patients who were included in and excluded from the analysis, with the exception that excluded patients attributed less physical symptoms to their kidney disease (illness identity; $t = -5.0$, $p < 0.01$). In the included sample, the mean age (SD) was 64.4 (14.0) years and the mean (SD) scores for physical and mental HRQOL were 54.6 (22.2) and 67.9 (20.4) respectively. All baseline characteristics are shown in Table 1.

During the first 18 months of predialysis care, 20 patients (5.1%) died, 6 patients (1.5%) experienced a recovered kidney function, 21 patients (5.3%) received a kidney transplant, 6 patients (1.5%) were transferred to a nonparticipating centre, 23 patients (5.8%) refused further participation, and 1 patient (0.3%) was censored for other reasons. Dialysis was initiated in 145 patients (36.6%; 84 patients [57.9%] started on haemodialysis, and 61 patients [42.1%] on peritoneal dialysis), and 174 patients (43.9%) still received predialysis care. The median [IQR] follow-up time in this sample was 16.1 [7.2 - 32.0] months).

Table 1. Baseline characteristics (N = 396)

Characteristic	
Demographic	
Age, years, mean ± SD	64.4 (14.0)
Sex, female, n (%)	135 (34.1)
Clinical	
Time since CKD diagnosis, median (IQR) years [a]	12.0 (9.0-20.0)
Diabetes mellitus, n (%)	101 (25.5)
Cardiovascular disease, n (%)	161 (40.7)
Body mass index (kg/m2), mean ± SD [b]	26.6 ± 5.0
eGFR (mL/min/1.73 m^2), mean ± SD [c]	16.8 ± 6.1
Serum albumin (g/L), mean ± SD [d]	40.9 ± 4.6
Haemoglobin (g/dL), mean ± SD [e]	12.3 ± 1.5
Psychosocial	
Physical HRQOL (range = 0 - 100), mean ± SD [f,h]	54.6 ± 22.2
Mental HRQOL (range = 0 - 100), mean ± SD [g,h]	67.9 ± 20.4
Illness identity (range = 0 - 14), mean ± SD [i]	3.1 ± 2.5
Timeline acute/chronic (range = 6 - 30), mean ± SD [i]	24.9 ± 4.2
Timeline cyclical (range = 4 - 20), mean ± SD [i]	11.3 ± 3.4
Negative consequences (range = 6 - 30), mean ± SD [i]	20.6 ± 4.1
Personal control (range = 6 - 30), mean ± SD [i]	18.0 ± 4.1
Treatment control (range = 5 - 25), mean ± SD [i]	15.2 ± 3.0
Illness coherence (range = 5 - 25), mean ± SD [i]	17.4 ± 4.1
Emotional response (range = 6 - 30), mean ± SD [i]	16.5 ± 5.3

Note. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables and as median (boundaries of interquartile range [IQR]) for skewed variables. Abbreviations: CKD, chronic kidney disease; HRQOL, health-related quality of life; eGFR, estimated glomerular filtration rate. For superscripts a through g, complete data available with the exception of the following variables with data available for [a] 381 (96.2%), [b] 388 (98.0%), [c] 351 (88.6%), [d] 325 (82.1%), [e] 349 (88.1%), [f] 384 (97.0%), and [g] 394 (99.5%). [h] Mean scores of the general Dutch population for physical and mental HRQOL are 76.3 and 77.9, respectively (these mean physical and mental HRQOL composite scores were calculated based on unstandardized mean scores of the 36-item Short Form Health Survey subscales described by Aaronson et al.[38]. [i] Higher scores on illness perception domains reflect that patients attribute more physical symptoms to their kidney disease (i.e., illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e., illness coherence).

Distinct physical HRQOL trajectory classes

A 3-class solution was found to fit the data adequately (see Table 2). The three identified classes of physical HRQOL are summarized in Table 3, and Figure 1A depicts the physical HRQOL trajectories. The first class, termed "low-stable" contained 34.1% of the patients, and was characterized by low levels of physical HRQOL that remained stable over time. The second class (32.5% of the sample), termed "medium-declining" was defined by a moderate level of physical HRQOL, which significantly worsened with time. The final class (33.4% of the patients) was a "high-increasing" class, and was characterized by a high level of physical HRQOL, which significantly increased over time.

Table 2. Latent class growth model fit specification for physical and mental HRQOL classes

	Number of classes			
Physical HRQOL (N = 384)	**1**	**2**	**3[a]**	**4**
Number of free Parameters	6	9	12	15
Log likelihood	-4162.26	-3978.54	-3931.15	-3920.26
Bayesian Information Criterion	8360.54	8011.10	7934.32	7930.55
Entropy		0.73	0.67	0.68
Vuong-Lo-Mendell-Rubin likelihood test for K-1 versus K classes, *p*-value		< 0.01	< 0.01	0.09
Mental HRQOL (N = 394)	**1**	**2[b]**	**3**	**4**
Number of free Parameters	6	9	12	15
Log likelihood	-4111.98	-3961.41	-3929.53	-3913.31
Bayesian Information Criterion	8235.96	7976.94	7931.21	7916.79
Entropy		0.76	0.67	0.63
Vuong-Lo-Mendell-Rubin likelihood test for K-1 versus K classes, *p*-value		< 0.01	0.36	0.03

Abbreviations: HRQOL, health-related quality of life. [a] A three-class solution had the best model fit as determined by the combination of the fit indices, and the average posterior probabilities for each trajectory class were higher than 0.70 (0.85, 0.77, and 0.90, respectively). [b] A two-class solution had the best model fit as determined by the combination of the fit indices, and the average posterior probabilities for each trajectory class were higher than 0.70 (0.91 and 0.94, respectively).

Distinct mental HRQOL trajectory classes

A two-class solution was deemed adequate for mental HRQOL (see Table 2). The two mental HRQOL classes are shown in Table 3, and Figure 1B depicts the mental HRQOL trajectories. The first class, termed "low-stable" contained 38.7% of the patients, and was characterized by low levels of mental HRQOL that remained stable over time. The second class, termed "high-stable" (61.3% of the sample), was defined by high levels of mental HRQOL that remained stable over time.

Table 3. Class solutions for physical HRQOL (n = 384) and mental HRQOL (n = 394) [a]

Class	Trajectory	Intercept	Slope [b]	n (%)
Physical HRQOL				
Class 1	Low-stable	32.45**	-0.86	131 (34.1)
Class 2	Medium-declining	57.10**	-3.91**	125 (32.5)
Class 3	High-increasing	75.28**	1.84*	128 (33.4)
Mental HRQOL				
Class 1	Low-stable	48.86**	-1.41	152 (38.7)
Class 2	High-stable	80.13**	-0.61	242 (61.3)

[a] The median (IQR) number of health-related quality of life (HRQOL) measurements was 2 (1 - 3) during the first 18 months of predialysis care. Physical and mental HRQOL scores available at follow-up were: 260 (67.7%) and 261 (66.2%) at 6 months, 169 (44.0%) and 168 (42.6%) at 12 months, and 102 (26.6%) and 102 (25.9%) at 18 months, respectively. [b] Change in HRQOL scores per 6 months during the first 18 months of predialysis care. * $P < 0.05$, ** $P < 0.01$.

Factors associated with physical HRQOL class membership

Of the demographic and clinical factors (age, gender, eGFR, BMI, DM, CVD, time since CKD diagnosis, serum albumin and haemoglobin) only age and CVD were significantly associated with physical HRQOL class membership: compared with the high-increasing physical HRQOL class (Class 3), a 1-year increase in age was associated with a 4% increase in the odds of being in the low-stable physical HRQOL class (Class 1; OR = 1.04, $p < 0.01$), and the presence of CVD was associated with a 2.1 times increase in the odds of being in the low-stable physical HRQOL class (Class 1; OR = 2.1, $p < 0.01$). Six out of the eight illness perception domains were also significantly associated with physical HRQOL class membership while adjusting for age, eGFR and comorbidities (see Table 4 for the crude and adjusted ORs). Increased odds for a low-stable physical HRQOL class (Class 1) were detected in patients who believed to a lesser extent that they can personally control their kidney disease and that they completely understand their kidney disease, compared with the high-increasing physical HRQOL class (Class 3). Put another way, a single point increase in personal control (higher control) reduced the odds of being in the low-stable class by 12% (OR_{adj} = 0.88, $p < 0.01$) and a single point increase in coherence (higher coherence) was associated with a 15% reduction in the odds of being in the low-stable class (OR_{adj} = 0.85, $p < 0.01$). Furthermore, compared with the high-increasing physical HRQOL class (Class 3), a one-point increase in illness identity, timeline cyclical, negative consequences and emotional response increased the odds of being in the low-stable physical HRQOL class (Class 1) by 50%, 36%, 14% and 7% respectively. Similarly, compared with the high-increasing physical HRQOL class (Class 3), a one-point increase in illness identity was associated with a 21% increase in the odds of being in the medium-declining physical HRQOL class (Class 2). Only trends were found for the odds of being in the medium-declining physical HRQOL class (Class 2) with regard to the illness perceptions timeline cyclical (OR_{adj} = 1.13, p = 0.06) and negative consequences (OR_{adj} = 1.14, p = 0.05) compared with the high-increasing physical HRQOL class (Class 3).

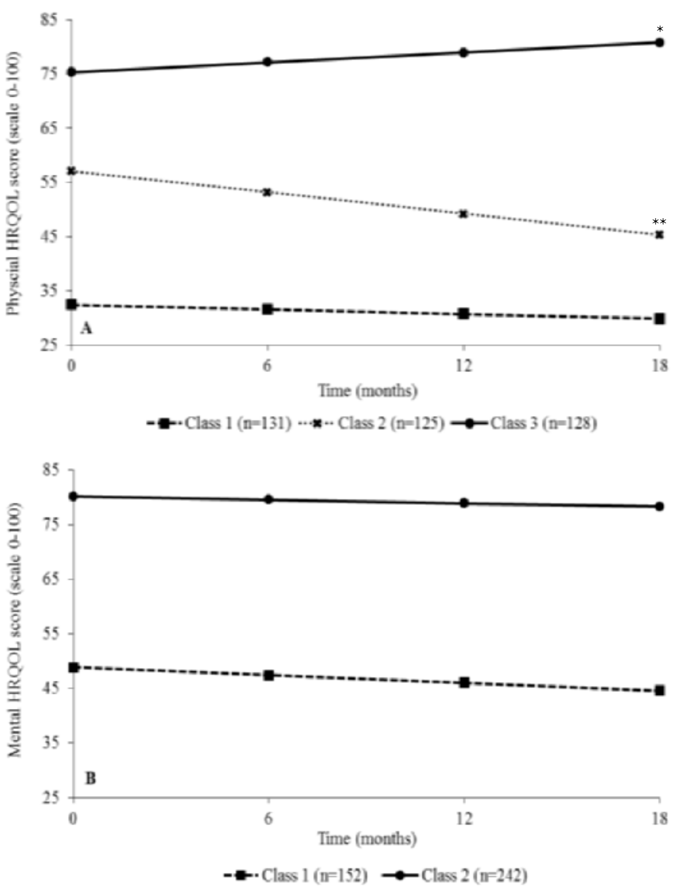

Figure 1. Distinct trajectories of health-related quality of life (HRQOL) during the first 18 months of predialysis care: three physical HRQOL trajectories (Panel A; n = 384), and two mental HRQOL trajectories (Panel B; n = 394). * $P < 0.05$. $^{**}P < 0.01$; significant change in HRQOL scores per 6 months during the first 18 months of predialysis care.

Table 4. Illness perception domains associated with physical HRQOL class membership (N = 384)

	Class 1 [a] Low-stable physical HRQOL		Class 2 [a] Medium-declining physical HRQOL	
	Unadjusted OR (95% CI)	Adjusted [b] OR (95% CI)	Unadjusted OR (95% CI)	Adjusted [b] OR (95% CI)
Illness identity	1.31 (1.18 to 1.46)**	1.50 (1.26 to 1.79)**	1.18 (1.03 to 1.34)*	1.21 (1.02 to 1.44)*
Timeline acute/chronic	0.98 (0.90 to 1.06)	0.98 (0.90 to 1.06)	1.03 (0.93 to 1.15)	1.05 (0.93 to 1.18)
Timeline cyclical	1.20 (1.05 to 1.35)*	1.36 (1.14 to 1.58)*	1.16 (1.06 to 1.27)**	1.13 (1.00 to 1.26)
Negative consequences	1.08 (1.01 to 1.16)*	1.14 (1.02 to 1.25)*	1.18 (1.08 to 1.23)*	1.14 (1.00 to 1.28)
Personal control	0.90 (0.82 to 0.98)*	0.88 (0.78 to 0.97)**	0.97 (0.89 to 1.06)	0.99 (0.90 to 1.08)
Treatment control	0.94 (0.77 to 1.12)	1.11 (0.97 to 1.24)	0.99 (0.88 to 1.09)	1.09 (0.96 to 1.23)
Illness coherence	0.83 (0.65 to 1.06)	0.85 (0.74 to 0.95)**	0.95 (0.81 to 1.12)	0.95 (0.86 to 1.03)
Emotional response	1.02 (0.97 to 1.08)	1.07 (1.00 to 1.15)*	1.05 (0.97 to 1.13)	1.05 (0.96 to 1.13)

Note. Higher scores on domains reflect that patients attribute more physical symptoms to their kidney disease (i.e., illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e., illness coherence). Abbreviations: OR, Odds ratio; CI, confidence interval. [a] Reference class: high-increasing physical health-related quality of life (HRQOL; Class 3). [b] Adjusted for age, kidney function, and comorbidities. * $P < 0.05$, ** $P < 0.01$.

Table 5. Illness perception domains associated with mental HRQOL class membership (N = 394)

	Class 1 [a] Low-stable mental HRQOL	
	Unadjusted OR (95% CI)	Adjusted [b] OR (95% CI)
Illness identity	1.24 (1.08 to 1.42)**	1.06 (0.80 to 1.26)
Timeline acute/chronic	0.98 (0.91 to 1.04)	0.99 (0.92 to 1.06)
Timeline cyclical	1.18 (1.09 to 1.28)**	1.22 (1.11 to 1.32)**
Negative consequences	1.10 (1.04 to 1.18)**	1.14 (1.05 to 1.23)**
Personal control	0.94 (0.88 to 1.00)	0.99 (0.92 to 1.06)
Treatment control	1.00 (0.93 to 1.09)	1.02 (0.93 to 1.10)
Illness coherence	0.86 (0.79 to 0.93)**	0.84 (0.76 to 0.93)**
Emotional response	1.06 (0.99 to 1.12)	1.07 (0.87 to 0.99)*

Note. Higher scores on domains reflect that patients attribute more physical symptoms to their kidney disease (i.e., illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e., illness coherence). Abbreviations: OR, Odds ratio; CI, confidence interval. [a] Reference class: high-stable mental health-related quality of life HRQOL; Class 2). [b] Adjusted for age, kidney function, and comorbidities. * $P < 0.05$, ** $P < 0.01$.

Factors associated with mental HRQOL class membership

None of the demographic or clinical factors (age, gender, eGFR, BMI, DM, CVD, time since CKD diagnosis, levels of serum albumin and haemoglobin) were significantly associated with mental HRQOL class membership. Four out of the eight illness perception domains were significantly associated with mental HRQOL class membership while adjusting for age, eGFR and comorbidities (see Table 5 for the crude and adjusted ORs). Compared with the high-stable mental HRQOL class (Class 2), a one-point increase in timeline cyclical, negative consequences and emotional response increased the odds of being in the low-stable mental HRQOL class (Class 1) by 22%, 14%, and 7%, respectively. Furthermore, increased odds for a low-stable mental HRQOL trajectory (Class 1) were detected in patients who believed to a lesser extent that they completely understand their kidney disease compared with the high-stable mental HRQOL class (Class 2). Put another way, a single point increase in coherence (higher coherence) was associated with a 16% reduction in the odds of being in the low-stable class ($OR_{adj} = 0.84$, $p < 0.01$).

Discussion

To the best of our knowledge this study is the first to examine distinct trajectories of HRQOL in patients receiving predialysis care using LCGM and to investigate which patient characteristics and illness perceptions at the start of predialysis care are associated with these specific HRQOL trajectories during predialysis care.

This study shows that distinct HRQOL trajectories can be detected during the first 18 months of predialysis care. Patients indeed differ to a large extent in their evaluation of HRQOL over time, and hence, underlines the importance of investigating heterogeneity of HRQOL in this population. Three physical HRQOL trajectories were observed, all containing approximately one third of our sample: a trajectory in which patients report stable levels of low physical HRQOL, a trajectory in which patients report moderate levels of physical HRQOL that worsened over time, and a trajectory in which patients report high levels of physical HRQOL that improved with time. Additionally, two mental HRQOL trajectories were identified: one trajectory containing approximately 60% of our sample in which patients reported stable high levels of mental HRQOL, and a second trajectory in which patients reported stable low levels of mental HRQOL. These results highlight that a large proportion of our sample has an unfavourable (i.e., stable low or declining) HRQOL trajectory during the first 18 months of predialysis care, which puts them at risk for adverse outcomes such as accelerated progression toward ESKD and mortality.[5,6] Furthermore, the findings that HRQOL remained rather stable in a large proportion of our sample could, to a certain extent, be considered remarkable as the predialysis phase is often considered a dynamic period. The predialysis phase is characterized by an accelerated disease progression, an intensified treatment to treat health complications and prepare patients for kidney replacement therapy (i.e., dialysis or transplantation), an increase in overt physical symptoms and drug-related side effects, and many patients perceive this phase as a stressful period during which they experience feelings as helplessness and hopelessness.[1,5,7,39,40] Therefore, one might expect that most patients report decreasing levels of physical and mental HRQOL during predialysis care and this expectation is also in line with previous studies that found decreased mean levels of HRQOL during predialysis care.[5] However, we did not find decreasing levels of physical and mental HRQOL in the majority of our sample and, although speculative, a possible explanation for our findings could be found in the phenomenon “response shift”. Response shift refers to a change in individuals’ meaning of HRQOL over time due to changes in their internal standard (e.g., a change in idea what poor health is), values (e.g., reprioritization the importance of certain life domains) and/or reconceptualization of the concept HRQOL.[41] These cognitive changes reflect patients’ adaptation to new situations, and could perhaps explain why patients’ evaluation of HRQOL did not decline but remained rather stable in a large proportion of our sample despite declining health. Finally, this stability in HRQOL seems particularly applicable to mental HRQOL: mental HRQOL remained rather stable in all patients while physical HRQOL remained stable in only one third of our sample. A possible explanation for this difference could be that predialysis care is relatively more focused on the treatment of the physical aspects compared with the mental aspects of the disease.[7,28]

Antecedent factors associated with different HRQOL trajectories were also examined in this study. The results showed that none of the demographic or clinical factors were associated with mental HRQOL class membership, however, age and CVD were associated with physical HRQOL class membership: increased odds for a low-stable physical HRQOL trajectory were detected in older patients and patients' diagnosis with CVD. In addition, six out of the eight illness perceptions were associated with HRQOL class membership; increased odds for both a low-stable physical and mental HRQOL trajectory were detected in patients who believed to a higher extent that their kidney disease has an unpredictable cyclical nature, has negative consequences upon their lives, causes emotional distress, and in patients who believed to a lesser extent that they fully understand their kidney disease. Additionally, increased odds for a low-stable physical HRQOL were detected in patients who believed to a lesser extent that they can personally control their disease, and increased odds of a low-stable and medium-declining physical HRQOL trajectory was detected in patients who attributed more physical symptoms to their kidney disease. These findings are in line with and builds on previous studies that found lower mean levels of HRQOL in patients with CKD associated with an older age,[4] CVD,[4,8] and stronger negative perceptions of illness, including illness identity, timeline cyclical, negative consequences, personal control, illness coherence and emotional response.[23-27]

An explanation for the relationship between illness perceptions and HRQOL found in this study can be derived from the Common Sense Model of self-regulation.[17,18] This theoretical framework suggests that patients' perceptions of illness shape their cognitive and behavioural adjustment to managing their illness (i.e., coping process and illness related behaviours) and consequently contribute to health outcomes. For our results, this could mean that patients with stronger negative illness perceptions deal with their kidney disease in more maladaptive ways (e.g., denial, nonadherence to treatment guidelines, and not seeking support), and consequently result in impaired or deteriorating HRQOL. Until now, the evidence for this explanation in patients with CKD is contradictory and limited to only a few cross-sectional studies; Knowles et al.[42] found (mal)adaptive coping to mediate the relationship between illness perceptions and psychological well-being, whereas Kim & Evangelista[34] did not find adherence to treatment guidelines to mediate the relationship between illness perceptions and clinical outcomes. Moreover, a recent meta-analysis also concluded that evidence for coping as a potential mediator in the relationship between illness perceptions and psychological health in people with other conditions was inconsistent.[43] Therefore, additional research is needed to further explore this potentially mediating role of coping and health behaviours in the relationship between illness perceptions and HRQOL trajectories during predialysis care.

Taken together, the results of this study suggest that in many patients physical and mental HRQOL remained compromised or became impaired during the first 18 months of predialysis care. Hence, implementing additional strategies at the start of predialysis care to support patients at risk for impaired HRQOL is required. Our results also suggest that illness perceptions are, compared with the demographic and clinical factors, most closely related to HRQOL trajectories. This latter finding is especially important because literature shows that unhelpful illness perceptions can be changed by means of psychoeducational interventions, and consequently improve outcomes.[44,45] Based on our results, key aspects of such interventions to optimize HRQOL in patients receiving predialysis care would be to target unhelpful beliefs about illness identity, timeline cyclical, negative consequences, personal control, illness coherence and emotional response. Examples of support strategies that could be implemented to target these unhelpful illness perceptions are: education (e.g., enhancing knowledge about kidney disease and how they can personally influence disease progression by adopting a healthy lifestyle), challenge misconceptions (e.g., about the unpredictable cyclical nature of CKD and related symptoms), and develop action plans (e.g., how to deal with emotional distress and the negative consequences that the disease has upon their lives, for instance by means of reattribution or increasing social support).[44,45] However, pilot studies are needed to evaluate if illness perception-based interventions would indeed improve HRQOL trajectories in patients receiving predialysis care.

The main strength of this study is the longitudinal instead of cross-sectional design that provided the opportunity to investigate changes in HRQOL over time. The PREPARE-2 dataset also offers information on a broad range of factors (i.e., HRQOL, illness perceptions, and variety of demographic and clinical factors) in a large sample of patients. A disadvantage of this observational design is that causal interpretation is still limited. Furthermore, a selection bias could have been introduced as not all eligible patients starting predialysis care have been included in this study (i.e., only patients who were asked and willing to participate). Potentially, unidentified confounding could also have led to biased results: that is, a decreased health status at the start of predialysis care could have caused both stronger negative illness perceptions and unfavourable HRQOL trajectories. However, we believe that we adequately adjusted for disease severity (i.e., age, kidney function, and comorbidities), and the results from the crude and adjusted analyses were very similar. Besides this, there is missing data as some patients did not (fully) complete the questionnaire (i.e., the questionnaire was not returned or insufficiently filled out), did not visit the predialysis outpatient clinic every 6 months or reached a study endpoint. However, it is unlikely that our missing data led to biased results, because little differences in baseline characteristics were observed between patients who were included in and excluded from the analyses. Moreover, to ensure maximum power and avoided bias estimates, missing data was treated using full-information maximum likelihood estimation, and there was no evidence that missing data was not random in nature. Finally, additional research is needed to confirm our results, to assess how HRQOL trajectories develop after 18 months of predialysis care, and to investigate if changes in illness perceptions would also lead to changes in HRQOL trajectories in patients receiving predialysis care.

Conclusions

Despite these limitations and the need for future research, this study identified various important markers for unfavourable HRQOL trajectories: an older age and the presence of CVD were associated with unfavourable physical HRQOL trajectories, and stronger negative perceptions of illness at the start of predialysis care were associated with unfavourable physical and mental HRQOL trajectories. Personalized treatment approaches to optimize HRQOL during predialysis care are desired and should take into account illness perceptions.

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Chapter 7

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

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Abstract

Objectives

Illness perceptions in patients with end-stage kidney disease are associated with nonadherence and increased mortality. However, no data are available regarding the relationship between illness perceptions and accelerated disease progression in predialysis patients.

Methods

A total of 416 incident predialysis patients participating in a prospective cohort (PREdialysis PAtient REcord-2 [PREPARE-2]) completed the Revised Illness Perception Questionnaire at the start of specialized predialysis care. The association between illness perceptions and time until start of dialysis was investigated using Cox regression models. Linear mixed modelling was used to test associations between illness perceptions and change of kidney function during predialysis care. Adjustments were made for sociodemographic, clinical, and biochemical factors.

Results

Five illness perceptions were associated with disease progression. Dialysis started earlier and kidney function declined faster (mL/min/1.73 m^2/year) in patients who perceived their kidney disease as being cyclical in nature (adjusted hazard ratio [HR_{adj}] = 1.32 [95% confidence interval {CI}, 1.11 to 1.56]; adjusted additional change = -0.64 [95% CI, -1.16 to -0.13]), having many negative consequences (HR_{adj} = 1.47 [95% CI, 1.18 to 1.85]; adjusted additional change = -0.67 [95% CI, -1.30 to -0.04]) and causing negative feelings (HR_{adj} = 1.21 [95% CI, 1.03 to 1.42]; adjusted additional change = -0.65 [95% CI, -1.13 to -0.16]). In addition, kidney function declined faster in patients who perceived that their kidney disease cannot be personally controlled (adjusted additional change = -0.69 [95% CI, -1.31 to -0.09]) and who perceived that they did not fully understand their kidney disease (adjusted additional change = -0.53 [95% CI, -1.05 to -0.01]).

Conclusions

Stronger negative perceptions of illness at the start of predialysis care are a marker for accelerated disease progression. Detecting illness perceptions in predialysis patients may provide opportunities to intervene and slow down disease progression.

Introduction

To make sense of their illness, patients create perceptions (i.e., representations or beliefs) about various aspects of their condition.[1] The Common Sense Model of self-regulation[2] postulates that these cognitive and emotional perceptions can affect how patients respond to the threat of illness, cope with the illness, and can subsequently determine health outcomes in different patient populations.[3,4] In patients with chronic kidney disease (CKD), illness perceptions have been associated with psycho-social outcomes (e.g., depression,[5,6] autonomy and self-esteem[7]), nonadherence to treatment (e.g., with regard to diet,[8,9] fluid intake,[10] and medication[8,11]), and health outcomes (e.g., health-related quality of life[12-16] and mortality[17]; see Chilcot[18]). To date, most studies have focused on patients with end-stage kidney disease (ESKD): an advanced stage of CKD in which patients' kidneys are no longer able to function and kidney replacement therapy (i.e., dialysis or transplantation) is necessary to survive. Little is known about illness perceptions in patients in an earlier stage of CKD, the predialysis phase (CKD stages 4 and 5), and it is important to address this research gap for several reasons.

First, during predialysis care, patients still have opportunities to slow down kidney failure and delay the progression toward ESKD (i.e., postponement of kidney replacement therapy) by active coping and responding adaptively. For example, adhering to pharmacotherapy and lifestyle restrictions may slow down disease progression in patients with CKD.[19-22] However, although the literature suggests that illness perceptions may play a vital role in determining health behaviours[8-11] and health outcomes[12-17] in patients with CKD, no research has been conducted to investigate whether illness perceptions are associated with disease progression in patients receiving predialysis care. By identifying illness perceptions in predialysis patients and associating them with disease progression, opportunities can be created to improve health outcomes in earlier stages of CKD and slow down the progression toward ESKD.

Second, it is assumed that illness perceptions are dynamic and are constantly updated according to new obtained knowledge and individual experiences.[23] Indeed, literature regarding patients with CKD has shown that illness perceptions change over time,[16] differ across and change according to clinical status and medical treatment,[12,13,24] and differ across the illness trajectory.[25] Consequently, it may not be accurate to assume that illness perceptions in patients with ESKD and their associations with outcomes also directly apply to illness perceptions in predialysis patients.

Therefore, the aims of this study are to identify illness perceptions in patients receiving specialized predialysis care and to investigate whether stronger negative perceptions of illness at the start of predialysis care are a marker for an accelerated disease progression, that is, an earlier start of dialysis and/or a faster decline of kidney function.

Methods

Study design

Data were collected in the PREdialysis PAtient REcord-2 study (PREPARE-2), a prospective cohort in the Netherlands. Between July 2004 and June 2011, incident predialysis patients were included at referral to 1 of 25 participating Dutch nephrology outpatient clinics. Patients were treated by their nephrologists according to the treatment guidelines of the Dutch Federation of Nephrology[19] (a guideline partly based on the Kidney Disease Outcomes Quality Initiative[20] and Kidney Disease Improving Global Outcomes[21] guidelines). Data were collected at the start of specialized predialysis care and every subsequent 6 months. Patients were followed up until the start of dialysis or censoring. Generally, the decision to initiate dialysis is based on a combination of clinical parameters (e.g., decline of kidney function to approximately 10 mL/min/1.73 m^2, hyperkalaemia, severity of uremic symptoms, and fluid overload) and the personal preference of the patient and the physician. Moreover, dialysis may be postponed due to vascular dementia or a life expectancy of less than 1 year.[19,26] Censoring was defined as follows: kidney transplantation, death, recovered kidney function, transferred to a nonparticipating centre, refused further participation, lost during follow-up, or end of follow-up (June 20, 2013). Approval of the Medical Ethics Committee or the institutional review board of all participating centres was obtained.

Patients

Adult patients (≥ 18 years) who were treated by a nephrologist and who have been recently (within the previous 6 months) referred to a specialized predialysis outpatient clinic (i.e., incident predialysis patients with progressive kidney failure and an estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2; CKD stages 4 and 5) were eligible for inclusion. Patients with a failing kidney transplant were also eligible for inclusion, if the transplantation was at least one year ago. Written informed consent was obtained from all participants before study inclusion.

Data, definitions, and measurements

Data were collected at the start of specialized predialysis care and at every subsequent 6-month interval. Laboratory data were extracted from the electronic hospital information systems or medical records. Kidney function was presented as the eGFR, using the abbreviated Modification of Diet in Renal Disease formula, taking into account age, sex, race (i.e., black), and serum creatinine.[27] Primary kidney disease was classified into four categories according to the codes of the European Renal Association - Dialysis and Transplantation Association registry (for more information on the diseases each category comprises, see http://www.era-edta-reg.org/prd.jsp).[28] All clinical measurements, including blood pressure, were measured according to the standard care in each outpatient clinic. Mental health was assessed by means of the five-item Mental Health Inventory of the 36-item Short Form Health Survey,[29] which can be used as a screening tool for depressive symptoms in dialysis patients.[30] Mental health scores ranged from 0 to 100, and a higher score implied less severe depressive symptoms. Furthermore, illness perceptions were assessed by means of self-report with the Revised Illness Perception Questionnaire (IPQ-R).[31] Using 38 questions, the following illness perception subscales were measured using a 5-point Likert scale ranging from 1 'strongly disagree' to 5 'strongly agree': timeline acute/chronic, timeline cyclical, negative consequences, personal control, treatment control, illness coherence, and emotional response. The 'illness identity' subscale, consisting of 14 items in a yes or no format, addresses different physical symptoms attributed to the kidney disease. In Table 1, the descriptions of the subscales are shown. Subscale scores were created following the official IPQ-R instructions.[31] A higher score on the IPQ-R subscales implied a greater perceived chronic or cyclical timeline, and a higher level of negative consequences, personal control, treatment control, illness coherence, emotional response, and identified symptoms. Like other studies assessing illness perceptions among patients with CKD,[8-10,14,32,33] illness perceptions regarding the 'cause of CKD' were not taken into account, due to the heterogeneous causes of CKD. The IPQ-R has been applied to patients with widely varying illnesses, including patients with CKD, and has satisfactory psychometric properties.[34] Cronbach alpha reliability coefficients were also calculated to test the reliability of the instrument in this predialysis population: all subscales demonstrated moderate to good reliability with Cronbach alpha values ranging from 0.63 to 0.90. In Table 1, the Cronbach alpha values regarding the IPQ-R subscales are shown.

Table 1. Revised Illness Perception Questionnaire subscales: descriptions and Cronbach alpha values (N = 416)

Illness perceptions [a]	Items (n)	Description	Alpha
Timeline acute/chronic	6	*Is my kidney disease permanent rather than temporary?*	0.82
Timeline cyclical	4	*Does my kidney disease and related symptoms have a cyclical nature?*	0.80
Negative consequences	6	*Does kidney disease have major consequences on my life?*	0.70
Personal control	6	*Can I influence kidney disease by how I personally behave?*	0.71
Treatment control	5	*Will my treatment be effective in controlling kidney disease?*	0.63
Illness coherence	5	*Do I have a complete understanding of my kidney disease?*	0.82
Emotional response	6	*Do I have lots of negative feelings about my kidney disease?*	0.90
Illness identity	14	*Which bodily symptoms are related to my kidney disease?*	N/A

N/A = not applicable. [a] All subscales are measured using a 5-point Likert scale, with the exception of 'illness identity' in which 14 symptoms were measured by using a yes or no format.

Statistical analyses

Descriptive statistics were computed to describe the patient baseline characteristics and illness perceptions. Dichotomous characteristics were presented as percentages, and continuous variables were presented as mean (standard deviation [SD]) for normally distributed variables and as median (boundaries of interquartile range [IQR]) for skewed variables. Chi-square tests of association and t-tests were conducted to evaluate whether patients who did complete the baseline IPQ-R questionnaire differ from patients who did not complete the questionnaire on sociodemographic, clinical and biochemical measures.

Cox proportional hazard regression analyses were applied to test the association between the separate continuous baseline illness perceptions and time until start of dialysis. Time zero in the analysis was the date the patient completed the IPQ-R questionnaire. Models were adjusted for baseline covariates including the following: age, sex, marital status, education, work status, primary kidney disease, time since diagnosis of primary kidney disease, body mass index, diabetes mellitus (type 1 or 2), cardiovascular disease (CVD; angina pectoris, coronary disease and/or myocardial infarction), serum albumin, haemoglobin, systolic and diastolic blood pressure, and eGFR. Linear mixed modelling was used to investigate the relationship between separate baseline illness perceptions and change of kidney function during predialysis care. In the model, we included the continuous baseline illness perceptions as the fixed independent variable, the variable time as a random variable, and the continuous kidney function as a dependent variable, with eGFR (i.e., kidney function) updated every 6 months. An interaction term was included in the model: illness perception * time, which indicated the additional change of kidney function with each unit increase on the illness perception subscale at the start of predialysis care. Adjustments were made for the following baseline covariates: age, sex, marital status, education, work status, primary kidney disease, time since diagnosis of primary kidney disease, body mass index, diabetes mellitus, CVD, serum albumin, haemoglobin, and systolic and diastolic blood pressure. All covariates in the regression models were examined for multicollinearity. Furthermore, because negative perceptions of illness are associated with increased depressive symptoms[5,6] and more severe depressive symptoms have been associated with an increased hazard for death in dialysis patients,[35,36] all analyses were repeated and additionally adjusted for baseline mental health. By adjusting for mental health, we gain insight into whether changes in disease progression were specific to illness perceptions or represent a broader underlying mental health condition. To prevent misunderstanding with regard to the results, we recoded the scores on the IPQ-R subscales ‘personal control’, ‘treatment control’ and ‘illness coherence’ in such a way that for all IPQ-R subscales a higher score implied a stronger negative perception of illness (i.e., higher scores now indicate a lower personal control, treatment control, and illness coherence). When information on covariates at the start of predialysis care was missing, data were imputed with multiple imputation (using 10 repetitions) to avoid loss of power and biased estimates: that is, when data are “missing at random” plausible estimates of missing data were calculated based on known characteristics of each patient.[37,38] In Table 2, the number of missing data is shown. The imputation model included the sociodemographic, clinical and biochemical characteristics described in Table 2, and additionally, the outcome reached (i.e., start of dialysis and follow-up time) as recommended.[39] A *p*-value of less than 0.05 was considered statistically significant, and all statistical analyses were performed using SPSS version 21.0.

Sensitivity analyses using a complete case approach were conducted as well. Moreover, Chi-square tests of association and t-tests were conducted to evaluate whether patients with missing covariates differ from patients without missing covariates (i.e., complete cases) on baseline characteristics measures and illness perception scores.

Results

Of the 502 included patients in the PREPARE-2 study, 416 patients had completed the baseline IPQ-R questionnaire and were included in the analyses. No significant differences were observed between sociodemographic, clinical and biochemical characteristics of patients who did complete the questionnaire and those who did not. At the start of predialysis care, the median (IQR) age was 68.5 (55.7 - 75.6) years, the mean (SD) eGFR was 16.8 (6.2) mL/min/1.73 m^2, and patients often had comorbid conditions: 25.5% of the patients were diabetic and 41.6% were diagnosed as having CVD. The baseline characteristics of the 416 included patients are presented in Table 2.

Illness perceptions in predialysis patients

The mean scores of the illness perceptions in Table 2 showed that at baseline, most of the mean scores laid around the midpoint of the scale (between 2.7 and 3.5 on a 5-point scale), with the exception that patients indicated that their kidney disease is chronic (mean [SD] score illness perception 'timeline acute/chronic' was 4.1 [0.7]). Moreover, the patients did not attribute many physical symptoms to their kidney disease (mean [SD] score illness perception 'illness identity' was 3.0 [2.5] of 14 symptoms). Furthermore, no significant differences in mean illness perception scores at baseline were observed between patients who eventually started haemodialysis and patients who started peritoneal dialysis, with the exception that peritoneal dialysis patients believed to a higher extent that their kidney disease can be personally controlled ($t = 2.22$, $p = .027$).

Table 2. Baseline characteristics and illness perceptions scores (N = 416) [a]

Characteristic	
Demographic	
Age, median (IQR) years	68.5 (55.7-75.6)
Sex, male, n (%)	276 (66.3)
Married or cohabiting, n (%) [*]	294 (70.7)
Education, low, n (%) [**]	252 (60.6)
Paid job, n (%) [***]	106 (25.5)
Clinical	
Primary kidney disease, n (%)	
Diabetes mellitus	56 (13.5)
Glomerulonephritis	59 (14.2)
Renal vascular disease	122 (29.3)
Other cause	179 (43.0)
Time since CKD diagnosis, median (IQR) years [□]	11.0 (8.0-19.8)
Body mass index, mean ± SD [□□]	26.7 ± 5.2
Diabetes mellitus, n (%)	106 (25.5)
Cardiovascular disease, n (%)	173 (41.6)
Systolic blood pressure (mm Hg), mean ± SD [ϕ]	142 ± 22
Diastolic blood pressure (mm Hg), mean ± SD [ϕ]	78 ± 12
Haemoglobin (g/dL), mean ± SD [†]	12.3 ± 1.5
Serum albumin (g/L), mean ± SD [‡]	40.8 ± 4.6
eGFR (mL/min/1.73 m^2), mean ± SD [Δ]	16.8 ± 6.2
Psychosocial [b]	
Mental health, mean ± SD [ω, c]	73.9 ± 17.3
Timeline acute/chronic, mean ± SD	4.1 ± 0.7
Timeline cyclical, mean ± SD	2.8 ± 0.8
Negative consequences, mean ± SD	3.4 ± 0.7
Personal control, mean ± SD	3.0 ± 0.7
Treatment control, mean ± SD	3.0 ± 0.6
Illness coherence, mean ± SD	3.5 ± 0.8
Emotional response, mean ± SD	2.7 ± 0.9
Illness identity, mean ± SD	3.0 ± 2.5

[a] Continuous variables are presented as mean ± SD for normally distributed variables and as median (IQR) for skewed variables. The characteristics presented are not imputed and available for: [*] 414, [**] 407, [***] 409, [□] 400, [□□] 408, [ϕ] 412, [†] 365, [‡] 338, [Δ] 368, [ω] 410 patients. [b] Illness perceptions are available for 416 patients. Possible range is 1 - 5 with the exception of the 'illness identity' subscale which has a possible range of 1 - 14. Note: A higher score on the IPQ-R subscales implies greater perceived timeline, negative consequences, personal control, treatment control, illness coherence, emotional response, and identified symptoms. [c] Mental health was assessed by means of the five-item Mental Health Inventory. Possible range of the mental health score is 0 - 100, with lower scores indicating more severe depressive symptoms.

Time until start of dialysis

The 416 patients were followed up for a median (IQR) of 15.5 (7.3 - 29.7) months, during which 29 patients (7.0%) died, 32 patients (7.7%) received a kidney transplant, 17 patients (4.1%) experienced a recovered kidney function, 48 patients (11.5%) refused further treatment, 8 patients (1.9%) were transferred to a nonparticipating centre, 4 patients (1.0%) were censored for other reasons, 55 patients (13.2%) were still receiving predialysis care, and in 223 patients (53.6%) dialysis had been initiated. Of the 223 patients who started dialysis, 138 patients (61.9%) started haemodialysis and 85 patients (38.1%) started peritoneal dialysis, and the median (IQR) follow-up time until dialysis initiation was 12.4 (5.3 - 21.9) months. Furthermore, at the initiation of dialysis, the mean (SD) eGFR was 10.5 (4.4) mL/min/1.73 m^2 and was not significantly related to illness perception scores at the start of dialysis (Pearson correlation coefficients did not exceed 0.13 and *p*-values ranged from .204 to .848).

In Table 3, the crude and adjusted hazard ratios (HRs) are shown for each unit increase on the IPQ-R subscales (5-point scale). Three illness perceptions were significantly associated with time until dialysis: dialysis started earlier among patients who believed to a higher extent that their kidney disease is cyclical in nature (crude HR = 1.24 [95% confidence interval {CI}, 1.06 to 1.46]), has many negative consequences (crude HR = 1.52; 95% CI, 1.24 to 1.85]), and cannot be personally controlled (crude HR = 1.23 [95% CI, 1.01 to 1.49]). After adjustment for demographic, clinical, and biochemical factors, most of the results did not change essentially, with the exception that the significant association between time until start of dialysis and 'personal control' was not found. However, after adjusting, a significant association with 'emotional response' was found: patients who believed to a higher extent that their kidney disease causes negative feelings started dialysis earlier (adjusted HR = 1.21 [95% CI, 1.03 to 1.42]). In addition, after adjustment for possible covariates and mental health, the results did not change essentially, with the exception that the association between time until start of dialysis and 'emotional response' was no longer found to be significant.

Association with change of kidney function during predialysis care

Of the 416 patients, 399 patients had at least one kidney function (eGFR) estimation and were included in this analysis (the previous imputed baseline kidney function measures were excluded as a covariate, as kidney function was the outcome measure in this analysis). The median number of eGFR measurements was 3 (IQR = 2 - 4), and the percentage of patients that only had one eGFR measurement available was 5.5%. The mean kidney function at baseline was 16.92 (95% CI, 16.28 to 17.56) mL/min/1.73 m^2, and the mean change of kidney function during predialysis care was -1.92 (95% CI, -2.35 to -1.50) mL/min/1.73 m^2/year. Furthermore, patients lost on average 19.8% of their kidney function during predialysis care.

Table 4 shows the crude and adjusted additional change of kidney function for each unit increase on the IPQ-R subscales (5-point scale) during predialysis care. Five illness perceptions at the start of predialysis care were related to a significant additional change of kidney function: an accelerated decline of kidney function was detected in patients who believed to a higher extent that their kidney disease is cyclical in nature (crude additional change = -0.63 [95% CI, -1.15 to -0.12] mL/min/1.73 m^2/year), cannot be personally controlled (crude additional change = -0.64 [95% CI, -1.26 to -0.03] mL/min/1.73 m^2/year), causes negative feelings (crude additional change = -0.64 [95% CI, -1.13 to -0.16] mL/min/1.73 m^2/year), and has many negative consequences (crude additional change = -0.68 [95% CI, -1.30 to -0.06] mL/min/1.73 m^2/year), and in patients who believed to a higher extent that they did not understand their kidney disease (crude additional change = -0.54 [95% CI, -1.06 to -0.01] mL/min/1.73 m^2/year). None of the results changed essentially after adjustment for sociodemographic, clinical, and biochemical factors and mental health.

Table 3. Association of baseline illness perceptions (5-point scale) with time until start of dialysis: crude, adjusted for covariates and mental health (N = 416)

Illness perception domains [a]	Model 1 [b] HR (95% CI)	Model 2 [c] HR (95% CI)	Model 3 [d] HR (95% CI)
Timeline acute/chronic	1.05 (0.86 to 1.28)	1.07 (0.86 to 1.34)	1.05 (0.84 to 1.30)
Timeline cyclical	1.24 (1.06 to 1.46)**	1.32 (1.11 to 1.56)**	1.26 (1.05 to 1.50)*
Negative consequences	1.52 (1.24 to 1.85)**	1.47 (1.18 to 1.85)**	1.34 (1.05 to 1.71)*
Personal control	1.23 (1.01 to 1.49)*	1.10 (0.89 to 1.35)	1.11 (0.90 to 1.37)
Treatment control	1.08 (0.87 to 1.35)	1.11 (0.88 to 1.40)	1.05 (0.83 to 1.34)
Illness coherence	1.09 (0.92 to 1.28)	1.13 (0.94 to 1.35)	1.04 (0.86 to 1.25)
Emotional response	1.11 (0.96 to 1.29)	1.21 (1.03 to 1.42)*	1.07 (0.88 to 1.29)
Illness identity	1.04 (0.99 to 1.09)	1.02 (0.97 to 1.08)	1.00 (0.94 to 1.06)

[a] Scores on the IPQ-R subscales 'personal control', 'treatment control', and 'illness coherence' were recoded: higher scores indicate lower personal control, treatment control and illness coherence. [b] Model 1: crude hazard ratio (HR) for each unit increase on the IPQ-R subscales. [c] Model 2: adjusted for age, gender, work status, marital status, education, primary kidney disease, time since diagnosis, CVD, diabetes mellitus, body mass index, serum albumin, haemoglobin, systolic and diastolic blood pressure and eGFR. [d] Model 3: Model 2 and further adjusted for mental health. * $P < 0.05$, ** $P < 0.01$.

Table 4. Association between baseline illness perceptions (5-point scale) with additional decline of kidney function per year: crude, adjusted for covariates and mental health (N = 399)

Illness perception domains [a]	Model 1 [b] additional change eGFR (95% CI)	Model 2 [c] additional change eGFR (95% CI)	Model 3 [d] additional change eGFR (95% CI)
Timeline acute/chronic	-0.07 (-0.71 to 0.57)	-0.05 (-0.68 to 0.59)	-0.05 (-0.68 to 0.59)
Timeline cyclical	-0.63 (-1.15 to -0.12)*	-0.64 (-1.16 to -0.13)*	-0.64 (-1.15 to -0.13)*
Negative consequences	-0.68 (-1.30 to -0.06)*	-0.67 (-1.30 to -0.04)*	-0.67 (-1.30 to -0.04)*
Personal control	-0.64 (-1.26 to -0.03)*	-0.69 (-1.30 to -0.09)*	-0.70 (-1.30 to -0.09)*
Treatment control	-0.46 (-1.15 to 0.23)	-0.33 (-1.02 to 0.37)	-0.33 (-1.02 to 0.36)
Illness coherence	-0.54 (-1.06 to -0.01)*	-0.53 (-1.05 to -0.01)*	-0.53 (-1.05 to -0.01)*
Emotional response	-0.64 (-1.13 to -0.16)*	-0.65 (-1.13 to -0.16)**	-0.65 (-1.14 to -0.16)**
Illness identity	-0.07 (-0.23 to 0.09)	-0.09 (-0.24 to 0.07)	-0.09 (-0.24 to 0.07)

[a] Scores on the IPQ-R subscales 'personal control', 'treatment control' and 'illness coherence' were recoded: higher scores indicate lower personal control, treatment control and illness coherence. [b] Model 1: crude additional change of kidney function for each unit increase on the IPQ-R subscale during predialysis care. [c] Model 2: adjusted for age, gender, work status, marital status, education, primary kidney disease, time since diagnosis, CVD, diabetes mellitus, BMI, serum albumin, haemoglobin, systolic and diastolic blood pressure. [d] Model 3: model 2 and further adjusted for mental health. * $P < 0.05$, ** $P < 0.01$.

Sensitivity analysis

The sensitivity analysis showed that most of the results remained stable when conducting the complete case analysis, with the exception that no significant association was found between time until start of dialysis and 'negative consequences' and 'emotional response' (adjusted HR [HR_{adj}] = 1.27 [95% CI, 0.96 to 1.67] and HR_{adj} = 1.16 [95% CI, 0.95 to 1.41], respectively). In addition, no significant associations were found between additional change of kidney function and 'timeline cyclical', 'negative consequences', 'personal control', and 'illness coherence' (adjusted additional change = -0.32 [95% CI, -0.85 to 0.22] mL/min/1.73 m^2/year, -0.36 [95% CI, -1.04 to 0.32] mL/min/1.73 m^2/year, -0.40 [95% CI, -1.07 to 0.27] mL/min/1.73 m^2/year, and -0.40 [95% CI, -0.96 to 0.16] mL/min/1.73 m^2/year, respectively). Furthermore, no significant differences were observed between patients with missing covariates and patients without missing covariates with regard to baseline characteristics measures and illness perception scores.

Discussion

This study assessed illness perceptions at the start of specialized predialysis care and found that stronger negative perceptions of illness are associated with an earlier start of dialysis and a faster decline of kidney function. More specifically, the analyses showed that five out of the eight illness perceptions were related to accelerated disease progression: dialysis started earlier and kidney function declined faster in patients who believed to a higher extent that their kidney disease is cyclical in nature (i.e., more unpredictable symptoms), has serious negative consequences upon their lives, and causes negative feelings (i.e., disease specific distress). In addition, kidney function declined faster in patients who believed to a higher extent that their kidney disease cannot be personally controlled and who believed they do not fully understand their kidney disease.

These findings build on and are in line with previous research that explored the relationship between illness perceptions and health outcomes in patients with CKD: stronger negative perceptions of illness including stronger perceptions of negative consequences, timeline cyclical, negative emotional response, and weaker perceptions of personal control and illness coherence have been associated with negative outcomes.[5-18] In contrast, studies that have examined the association between illness perceptions and mortality in dialysis patients only found a significant relationship with the belief that their treatment is effective in controlling their kidney disease.[32,33] This discrepancy cannot be explained by differences in mean illness perception scores between the two populations; in contrast to what literature suggests,[12,13,24,25] we did not observe large differences between predialysis and dialysis patients' illness perceptions with the exception that predialysis patients attribute less symptoms to their disease (i.e., illness identity). However, it is possible that the association between illness perception 'treatment control' and clinical health outcomes (e.g., mortality) may be more pronounced in the dialysis setting because not fully engaging with the dialysis regimen and associated medication and dietary requirements would have more proximal implications regarding clinical events and outcomes. Furthermore, the accelerated disease progression seems to be uniquely related to stronger negative illness perceptions instead of being related to a broader underlying negative mental health condition. After adjustment for mental health, illness perceptions remained significantly related to disease progression, with the exception of the association between illness perception 'emotional response' and time until start of dialysis. The latter could be due to the conceptual overlap between these constructs (i.e., both measuring intense emotion reactions; Pearson correlation coefficient = -0.56, p = .000).

According to the Common Sense Model of self-regulation,[2] a possible explanation for the relationships found in this study could be that stronger negative perceptions about the disease influence the extent to which patients feel motivated and capable to regulate their illness and adhere to recommended treatment guidelines. Presumably, this could mean that illness perceptions are associated with disease progression, mediated via nonadherence to medication and lifestyle guidelines. This hypothesis is supported by studies among patients with advanced CKD that show that illness perceptions are associated with nonadherence to treatment[8-11] and that adherence to multiple lifestyle guidelines (e.g., low-sodium diet[40] and not smoking[41]) can play a protective role in disease progression of patients with CKD.[22] However, it was not possible to explore this suggested mechanism in our study because adherence was not measured. Moreover, until now, there is only limited evidence: to our knowledge, this mechanism has only been identified in a few studies among patients with chronic illness[42,43] but not in patients with CKD.[9]

Therefore, additional research is needed, to investigate whether adherence indeed mediates the effect of illness perceptions on health outcomes in patients with CKD and also to replicate the results found in this study. This is especially important because – in contrast to many medical factors that influence the progression of kidney disease and the initiation of dialysis – illness perceptions are modifiable; the literature has shown that interventions aimed at changing illness perceptions can indeed improve health outcomes in patients with a chronic disease. For instance, altering illness perceptions resulted in better adherence to fluid intake in haemodialysis patients,[44] improved beliefs and knowledge about their treatment in haemodialysis patients,[45] and resulted in better functional outcome and an earlier return to work in patients recovering from a myocardial infarction.[46] In renal care, it is therefore important that health care professionals identify patients' illness perceptions, for instance, with the Brief Illness Perception Questionnaire.[47] On the basis of patients' responses on the illness perception scales, illness perceptions and coping strategies can be discussed and, if needed, additional interventions should be provided. These interventions could encompass different strategies[44-46,48]: for instance, additional education (e.g., about the effects of the treatment or lifestyle on retaining kidney function), discussing misconceptions (e.g., about the course and symptoms of CKD), self-monitoring and personal goal setting (e.g., with regard to changing lifestyle), or developing personalized coping plans to deal with negative emotional beliefs and negative beliefs about consequences of the disease (e.g., how to turn negative thoughts into constructive ones or increasing social support). Initiatives for developing and implementing interventions aimed at changing illness perceptions have been undertaken in patients with ESKD but should also be undertaken in earlier stages of the CKD aimed at slowing down disease progression.[48]

A great strength of the PREPARE-2 study is the prospective, longitudinal nature of this study that results in kidney function measures for every 6-month interval during predialysis care, and hence, changes over time can be investigated. A disadvantage of our study is missing data because some patients did not visit the predialysis outpatient clinic every 6 months, and data were only collected and checked periodically. These missing data could, possibly, lead to biases. First, only 416 patients of 502 patients completed the baseline IPQ-R questionnaire, and second, for a small percentage of patients, baseline characteristics were missing (8.3%). However, it is unlikely that this has led to biased results because no baseline sociodemographic, clinical, and biochemical differences were observed between patients who did and those who did not complete the questionnaire. Moreover, missing baseline data were imputed as we do not believe "missing not at random" is dominant is this sample. The sensitivity analysis showed that most of the results before and after imputations remained similar, but some differences were detected. These differences are most likely not due to a selection bias – given that there were no differences detected between the complete and noncomplete cases with regard to baseline characteristics measures and illness perception scores – but due to the loss of power in the complete case analysis by not including patients with missing baseline covariates.[37] A limitation regarding the generalization should also be addressed: in this sample, the percentage of patients with diabetes mellitus as primary cause of kidney disease is representative for the Netherlands and many European countries, but is considerably lower compared with percentages in, for instance, the

United States or Asia.[49] Furthermore, causal interpretation is limited due to the observational design of this study and the possibility of unidentified confounding. Although adjustments were made for many relevant confounders, it is possible that we did not adjust for illness severity sufficiently; if patients were actually sicker at the start of predialysis care, this could have caused both stronger negative perceptions of illness during predialysis care and an earlier start of dialysis or a faster decline of kidney function. However, the results from the crude and adjusted analysis were remarkably similar despite adjusting for a broad range of potential sociodemographic, clinical, and biochemical confounders. This makes it less likely that we missed important confounders. Finally, additional research is needed: studies that investigate the evolvement of illness perception during predialysis care and randomised controlled trials to assess whether interventions aimed at modifying negative illness perceptions lead to an earlier start of dialysis and a faster decline of kidney function during predialysis care.

Conclusions

Illness perceptions are associated with disease progression in patients with CKD on predialysis care. The relationship found indicates that stronger negative perceptions of illness at the start of specialized predialysis care can be an important marker for an earlier start of dialysis and a faster decline of kidney function. Detection of illness perceptions in predialysis patients may provide opportunities to intervene and improve health outcomes in predialysis patients.

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Chapter 8

Summary and general discussion

Introduction

Individuals with chronic kidney disease (CKD) suffer from a gradual and permanent loss of kidney function. As CKD progresses, the impact of the disease on patients' lives and health care costs increases,[1,2] and thus, strategies to slow down disease progression in early stages of CKD are crucial. Reducing sodium intake has been identified as an important treatment strategy to improve health outcomes in patients with CKD; however, most patients with CKD do not reach the sodium-target.[3] Therefore implementing additional support strategies into nephrological care is urgently needed,[3,4] but in order to design effective strategies, knowledge about patients' experiences with reducing sodium intake (e.g., perceived barriers) and about their needs and preferences regarding support strategies is required. Furthermore, literature suggests that theory-based self-regulation interventions encompassing multiple behaviour change techniques are needed to successfully change health behaviours,[5-8] but such interventions aimed at supporting early stage CKD patients in reducing their sodium reduction have not yet been developed and evaluated.

For patients receiving predialysis care, in addition to the importance of slowing down disease progression, strategies to retain an optimal health-related quality of life (HRQOL) are also indispensable. However, it is unclear which patients could benefit most from additional support strategies to improve HRQOL during predialysis care and the treatment guidelines provide little guidance on how to improve an impaired HRQOL.[9] A medical approach that has been identified as a strategy to improve HRQOL, is the use of anaemia medication. However, the optimal haemoglobin (Hb) treatment target is unknown; striving for high levels of Hb using anaemia medication can increase HRQOL,[10] but can also increase the risks for adverse health outcomes.[11] Research investigating the combined association of Hb levels and anaemia medication with HRQOL is therefore warranted, and this research should also explore if these associations differ depending on patients' characteristics (e.g., age).[12,13] Furthermore, non-medical approaches to improve both HRQOL and disease progression should be explored as well. A large body of literature shows that illness perceptions are key to understanding outcomes in different patient populations,[14] and that psychological interventions aimed at changing illness perceptions can result in improved outcomes.[15,16] In patients with end-stage kidney disease (ESKD), illness perceptions are associated with various outcomes (e.g., HRQOL[17-21] and mortality[22]), but little is known about the role that illness perceptions play in HRQOL and disease progression in patients receiving predialysis care.

The above makes clear that important steps are still to be taken to slow down disease progression and optimize HRQOL in patients with CKD prior to ESKD. This dissertation aimed to identify opportunities for improving patient care by using a biopsychosocial, patient-centred and self-regulation perspective.

Biopsychosocial perspective

The biopsychosocial model was introduced to encourage medicine to expand its rather narrow biomedical approach towards health and disease. The model proposes that, in order to improve health outcomes and alleviate distress of patients, clinicians must attend not only to the biological dimensions of illness, but also to the psychological and social domains.[23] This more holistic approach toward medicine in which patients' subjective experiences and behaviours are at the centre of interest, has been embraced and endorsed worldwide.[24]

Patient-centred perspective

Patient-centred care is often described as "care organized around the patients […] in which providers partner with patients and families to identify and satisfy the full range of patient needs and preference" (Frampton et al., 2008, p. 4).[25] Patient-centred care is also desired by many patients,[1,26,27] and to provide such care, it is important that, among other things, professionals take a biopsychosocial approach, patients' needs and concerns are explored, attention is being paid to health promotion, and that patients and professionals find common ground regarding management of the disease and have a good relationship.[28]

Self-regulation perspective

Self-regulation[5,29–33] can be described 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).[34] These human actions and steering processes are crucial for successful behaviour change and include different self-regulation skills (e.g., self-monitoring) and cognitions (e.g., illness perceptions). Self-regulation theory is a commonly used psychological framework for understanding health behaviours and from which effective support strategies can be derived.[5]

These three perspectives were applied throughout this dissertation by identifying patients' experiences, preferences and needs; evaluating the effectiveness of a patient-centred self-regulation intervention; exploring possibilities for individualized treatment approaches; examining the role of illness perceptions in HRQOL and disease progression; and continuously investigating relationships between factors and outcomes from different domains (e.g., demographic, clinical and psychosocial).

In this final Chapter of the dissertation, a summary of the main findings will be provided; first, three studies that focused on self-managed sodium reduction in early CKD stages (i.e., CKD stages 1 to 3) will be discussed, followed by the discussion of three studies that focused on various factors associated with disease progression and HRQOL in patients receiving predialysis care (CKD stages 4 and 5). Hereafter, a general discussion of our main findings, and of the strengths and limitations of the research contained in this dissertation will be offered. Finally, recommendations for future research and practice will be made.

Summary of the main findings

Part one: sodium reduction in early stages of CKD

Chapter 2 described the results of a qualitative study aimed at exploring patients' experiences when striving to adhere to a low-sodium diet, and at identifying perceived barriers and potential support strategies for reducing sodium intake. Eight focus groups were conducted with 25 patients with CKD and 23 health care professionals from four Dutch medical centres. The results showed that patients with CKD face multiple barriers when they try to limit their sodium intake, including the high sodium content in foods, and a perceived lack of knowledge, motivation, goal setting, coping skills, support, and feedback (e.g., regarding sodium intake and disease progression). Implementing additional support strategies into nephrological care is therefore warranted, and special attention should be paid to: providing practical information, setting personal sodium-related goals, discussing strategies on how to reduce sodium intake, increasing self-monitoring possibilities and social support, strengthening intrinsic motivation, and building a professional-patient relationship encompassing coaching and shared decision making. Additionally, to successfully maintain a low-sodium diet, environmental interventions are needed to reduce the high sodium content in products.

Chapter 3 reported on the results of a cross-sectional study to assess the importance of the previously identified sodium reduction barriers (see Chapter 2), and identify patient characteristics associated with sodium reduction barriers. Data (i.e., data from a questionnaire survey and medical records) of 156 patients with CKD from one Dutch medical centre were analysed, and the results confirmed that, in a broader CKD population, patients also experience multiple important sodium reduction barriers. With factor analysis, nine domains were identified, and correlation analysis showed that barriers perceived as most important were: the high sodium content in products, the lack of goal setting and discussing strategies for reducing sodium, not experiencing CKD-related symptoms yet, and the lack of feedback on sodium intake. Other barriers (coping skills when eating out, attitude, knowledge, and professional support) were rated as moderately important, and the barrier 'intrinsic motivation' was rated as somewhat important. Furthermore, patients differed (i.e., differences with regard to age, level of education, number of comorbidities, perceived autonomy support from professionals, depressive symptoms and self-efficacy) in the extent to which they experienced sodium reduction barriers, and patients with lower levels of self-efficacy and perceived autonomy support experienced most sodium reduction barriers. These findings indicate that patients with CKD could benefit from environmental interventions that reduce sodium levels in products, and from support strategies in nephrological care that help patients to overcome the various important sodium reduction barriers, and strengthen patients' beliefs regarding self-efficacy and autonomy.

Chapter 4 described the results of the Effects of Self-Monitoring on Outcome of Chronic Kidney Disease (ESMO) study, an open randomised controlled trial to evaluate the effectiveness of an self-regulation intervention to support patients with CKD in reducing their sodium intake. In total, 151 patients with CKD from four Dutch medical centres were randomly assigned to the control group (i.e., regular care) or the intervention group (i.e., regular care plus a three-months self-regulation intervention). The intervention consisted of education, motivational interviewing, coaching, and self-monitoring of blood pressure and sodium intake. The findings showed that, at three months, the intervention resulted in reduced sodium excretion, daytime ambulatory diastolic blood pressure, diastolic office blood pressure, protein excretion, body weight and improved self-efficacy compared to regular care. At six months, differences in sodium excretion and ambulatory blood pressures between the groups were not significant anymore, but the beneficial effects on systolic and diastolic office blood pressures, protein excretion, body weight and self-efficacy were maintained. No treatment effects in kidney function, antihypertensive medication and HRQOL were found. Furthermore, patient satisfaction with the intervention was high and all intervention components were evaluated as very useful. These findings indicate that, compared to regular care only, this self-regulation intervention modestly improved outcomes, although effects on primary outcomes waned over time.

Part two: HRQOL and disease progression during predialysis care

Chapter 5 described the results of a longitudinal study examining the combined association of different Hb levels and prescription of anaemia medication (erythropoietin-stimulating agent [ESA]/iron) with HRQOL in elderly (≥ 65 years) compared with young (< 65 years) patients during the first 2 years of predialysis care. A total of 371 patients participating in the PREdialysis PAtient REcord-2 (PREPARE-2) study were included in this analysis, and the results showed that the associations between Hb levels and HRQOL differ by age and by the use of anaemia medication. Compared to elderly patients with Hb levels on the current treatment target (≥ 11 to < 12 g/dL), elderly patients with high Hb levels (≥ 13 g/dL) without prescribed medication had higher levels of physical and mental HRQOL. This association between high Hb levels and higher levels of HRQOL was not found in elderly patients who were prescribed anaemia medication. In younger patients, higher levels of physical and mental HRQOL were also detected in patients with high Hb levels, but only in patients who were prescribed medication. These findings suggest that striving for high Hb levels using anaemia medication could increase HRQOL in younger patients receiving predialysis care, but not in elderly.

In **Chapter 6** we reported on the findings of a longitudinal study to examine distinct HRQOL trajectories during the first 18 months of predialysis care, and identify associated patient characteristics and illness perceptions at the start of predialysis care. In total, 396 patients participating in the PREPARE-2 study were included in the analysis and the results showed that patients differed in their HRQOL evaluation over time. With latent class growth analysis, three physical HRQOL trajectories (i.e., high-increasing, medium-declining, and low-stable) were identified, all containing approximately one-third of the sample. Two mental HRQOL trajectories were detected: a high-stable trajectory containing approximately one-third of the sample, and a low-stable trajectory containing approximately two-third of the sample. Furthermore, the following markers for unfavourable (i.e., low-stable or medium-declining) HRQOL trajectories were identified: an older age and the presence of cardiovascular disease were associated with unfavourable physical HRQOL trajectories, and stronger negative perceptions of illness (i.e., beliefs regarding timeline cyclical, illness identity, personal control, illness coherence, negative feelings and consequences) were associated with unfavourable physical and mental HRQOL trajectories. These findings suggest that many patients have an unfavourable HRQOL trajectory, and that personalized strategies to support patients at risk for impaired HRQOL during predialysis care are desirable, and should take into account illness perceptions.

Chapter 7 described the results of a longitudinal study to investigate the relationship between illness perceptions and disease progression (i.e., change in kidney function and time until start of dialysis) during predialysis care. In total, 416 patients participating in the PREPARE-2 study were included in this analysis and the results showed that five illness perceptions were associated with disease progression. Kidney function declined faster and dialysis started earlier in patients who believed to a higher extent that their kidney disease has an unpredictable cyclical nature, causes emotional distress and has many negative consequences upon their lives. Additionally, kidney function declined faster in patients who believed to a higher extent that they do not fully understand their kidney disease and in patients who believed to a higher extent that their kidney disease cannot be personally controlled. These findings suggest that stronger negative perceptions of illness are a marker for accelerated disease progression during predialysis care. Detection of unhelpful illness perceptions in patients receiving predialysis care may provide opportunities to intervene and slow down disease progression during predialysis care.

General discussion

For the results of each study included in this dissertation, a separate discussion is provided in the corresponding Chapters (see Chapters 2 to 7). In this section of the dissertation, a more overarching discussion of the main findings in light of the biopsychosocial, patient-centred and self-regulation perspectives will be provided.

Sodium reduction in early stages of CKD

Changing health behaviours is notoriously difficult to achieve and non-compliance to treatment is extremely high in patients with a chronic disease.[35,36] This also seems applicable for sodium reduction in patients with CKD as most patients do not reach the sodium-target.[3,4]

Patients' experiences

In Chapters 2 and 3 of this dissertation we identified multiple important barriers that patients with CKD face when they try to limit their dietary sodium intake, thereby providing us with explanations for *why* so many patients do not succeed in adhering to a low-sodium diet. The findings from both chapters also underline the importance of several self-regulation principles in sodium reduction among patients with CKD. A central tenet in self-regulation theories is that behaviour is a dynamic goal-process that can be divided into a motivational phase (i.e., goal selection and setting), an action phase (i.e., goal pursuit), and a maintenance phase (i.e., goal maintenance or disengagement). To go through these phases of behaviour change, both cognitions and skills play a key role, including goal setting, anticipatory coping, coping strategies, self-monitoring, feedback, and adaptive cognitions (e.g., self-efficacy, autonomous motivation and illness perceptions).[5,29,32,33,37]

In the qualitative study (Chapter 2), patients and professionals identified multiple sodium reduction barriers across all three phases of behaviour change and several barriers correspond with important self-regulation aspects, namely a perceived lack of intrinsic motivation, perceived personal control, goal setting, action planning, self-monitoring, feedback, and coping skills. The importance of these self-regulation aspects were also partly confirmed in Chapter 3; this cross-sectional study showed that patients believed that a lack of feedback on sodium intake, goal setting and discussing sodium reduction strategies were very important sodium reduction barriers, that lack of coping skills when eating out was a moderately important sodium reduction barrier, and that a lack of intrinsic motivation was a somewhat important sodium reduction barrier. Furthermore, self-regulation theory suggests that self-efficacy beliefs (i.e., one's belief that one is capable of performing a certain behaviour), are important when changing health behaviours.[29,38,39] The findings in Chapter 3 are in line with this suggestion, because, compared to all other factors (i.e., demographic, clinical and psychosocial factors), self-efficacy was most closely related to experiencing sodium reduction barriers: patients who believed to a lesser extent that they are capable to manage their disease, experienced more barriers when limiting dietary sodium, including a perceived lack of knowledge, feedback on sodium intake, and coping skills when eating out, and also expressed a more negative attitude towards a low-sodium diet.

Taken together, the results described in Chapters 2 and 3 show that, in line with self-regulation theory,[5] reducing sodium intake is not solely a matter of 'will', but that various cognitions and skills play a vital role in successfully incorporating the sodium treatment guidelines into one's life.

Potential support strategies in nephrological care

The results described in Chapters 2 and 3 also indicate that patients with CKD could benefit greatly from additional support when striving to adhere to a low-sodium diet. Given the large amount of sodium reduction barriers that patients encountered and considered to be important, it is also imperative that this support is not limited to one single strategy at a fixed moment during treatment. On the contrary, the implementation of a multifaceted approach is required to help patients successfully go through the different phases of behaviour change,[5] and special attention should be paid to the following self-regulation skills and cognitions: strengthen goal ownership and self-efficacy beliefs, increase coping skills, facilitate goal setting and action planning, and stimulate self-monitoring to obtain feedback. The results also indicate that the support should be patient-centred (e.g., 'building a patient-professional relationship that includes coaching and shared decision making' was identified as a potential support strategy in Chapter 2) and should encourage patients to be autonomous (e.g., patients who believed that they receive insufficient autonomy support from professionals experienced more sodium reduction barriers – see Chapter 3). These results suggest that the patient-centred techniques of motivational interviewing can contribute to effective patient support because fundamental aspects of motivational interviewing are fostering a collaborative relationship (e.g., not taking up the 'expert' role), drawing out the patients' own reasons to change (instead of professionals imposing their ideas), and commitment to the ultimate autonomy of the patients (recognise that the power to change lies within the patient).[40]

This need for a multicomponent patient-centred self-regulation intervention to adequately support patients with CKD in reducing their sodium intake is also in line with previous research that suggests that patient-centred[41–44] and self-regulation interventions that encompass multiple behaviour change techniques[6,8,45–47] can successfully improve health behaviours and outcomes in different populations. In patients with CKD, self-regulation interventions resulted in beneficial effects with respect to medication and fluid adherence,[16,48–50] but evidence for the effectiveness of self-regulation interventions for sodium reduction is lacking. Until now, sodium studies are limited to crossover trials (i.e., trials that evaluate the efficacy of brief and strictly regulated interventions without a behavioural approach)[51–54] and a few pragmatic trials that lacked a theoretical basis, were mainly education-based, and included only a few behaviour change techniques.[55,56]

Self-regulation support in nephrological care: design

We designed a three-month patient-centred intervention to support patients with CKD in reducing their daily sodium intake (see Chapter 4) and this intervention encompassed various evidence-based behaviour change techniques,[5,6,57–59] was based on self-regulation theory,[5] and addressed important sodium reduction barriers and associated factors (e.g., self-efficacy) as identified in Chapters 2 and 3. The sodium intervention started with a face-to-face motivational interview[40] in which the starting point were each patient's unique perspective, needs, and readiness to change. This interview aimed to strengthen adaptive self-regulation cognitions (e.g., self-efficacy, goal ownership, and illness beliefs [e.g., patients' belief of personal control and illness coherence]), and included various strategies such as: weighing pros and cons of (not) eating less sodium, exploring autonomous (i.e., self-chosen and personally important) reasons for reducing sodium intake, setting concrete and achievable goals that fit patients' personal life and long-term goals (e.g., remain independent as long as possible), rating the importance and confidence with regard to sodium reduction, discussing positive experiences with past behaviour change, discussing barriers for reducing sodium intake and possible strategies to cope with these difficulties, planning social support, and prompting self-reward. At the end of this interview, patients received education (e.g., information about the disease, treatment, and sodium intake) and a kidney-friendly cookbook. If desired, patients also received additional information about social support, refusal skills, medication adherence strategies, healthy eating, smoking cessation, increasing physical exercise and reducing alcohol intake. Hereafter, patients monitored their behaviour (e.g., dietary behaviour) and outcomes (e.g., blood pressure and urinary sodium excretion) at home, and had regular feedback-consultations with their coach by phone during which progression, achievements, barriers and possible solutions were discussed. After three months, a final face-to-face motivational interview took place that focused on evaluation (e.g., goal review and satisfaction with the new behaviour), and relapse prevention.

Self-regulation support in nephrological care: effectiveness

With this patient-centred self-regulation intervention we aimed to provide patients with the support they need to overcome the sodium reduction barriers and incorporate the sodium treatment guidelines into their daily life. Furthermore, a biopsychosocial approach was taken with regard to the study outcomes by not only assessing whether the intervention led to improved biomedical outcomes, but also psychosocial outcomes. Our findings (see Chapter 4) showed that patients greatly appreciated the support they received and that patients believed that the intervention was very useful. Furthermore, the results showed that the intervention resulted in various modest beneficial effects: improvements were found for sodium excretion, blood pressure measures (ambulant and office measures), protein excretion, body weight, and self-efficacy directly after the intervention. The intervention effects on office blood pressures, protein excretion, body weight and self-efficacy were also maintained until the 6 months follow-up. These results suggest that a biopsychosocial, patient-centred, and self-regulation approach may be effective to reduce sodium intake and improve outcomes in patients with CKD, although effects on the primary outcomes (sodium excretion and ambulant blood pressures) diminished over time.

Providing one clear explanation for the intervention effects is difficult. Firstly, because of the design of this study: we evaluated the effectiveness of a multicomponent intervention with only two groups (i.e., one group that received regular care and one group that received regular care plus the intervention), and thus, it is not possible to assess which intervention components were responsible for the intervention effects. Secondly, extensive questionnaires measuring multiple self-regulation skills (e.g., the Self-Regulation Skills Battery[60]) were not included in this study, and therefore, insight into the self-regulation process and the role of intermediate self-regulation variables is limited. However, one important self-regulation cognition was included as outcome in our study, namely self-efficacy beliefs. Self-efficacy beliefs are thought to influence the adoption and maintenance of goals, and to help patients to persevere despite the difficulties they encounter when trying to reach their goals. According to Bandura, self-efficacy beliefs are influenced by performance accomplishments, vicarious experiences, verbal persuasion, and emotional arousal.[29,38] In our study we aimed to increase self-efficacy beliefs by means of different support strategies (e.g., 'discussing past successes with regard to behaviour change', 'barrier identification and identify ways for overcoming them', 'action planning to achieve personal and achievable goals', and continuous 'feedback' throughout the intervention), and the results in Chapter 4 showed that our intervention indeed increased patients' self-efficacy beliefs. Given that self-efficacy beliefs are associated with self-care behaviours and with various outcomes in different patient populations including patients with ESKD,[39,61–63] it is possible that self-efficacy beliefs played a mediating role in our intervention effects.

From a theoretical point of view, there are also potential explanations for why some intervention effects waned over time. First, according to self-regulation theory,[5] behaviour is feedback-controlled and feedback mechanisms such as self-monitoring are considered important for successful behaviour change[6,8,57]: self-monitoring triggers people to (re)focus their attention towards the goal pursuit, provides people with information about whether they are 'on track' with regard to their goals, and guides subsequent actions (e.g., adjust strategies or goals based on feedback). Moreover, Chapters 2 and 3 also showed that patients with CKD perceived a lack of feedback on their sodium intake as one of the most important sodium reduction barriers and that they desire additional feedback. In order to facilitate sufficient feedback, patients in our study were prompted to monitor their sodium intake and associated health outcomes regularly. However, patients encountered problems with two self-monitoring tools (i.e., the online diary was complex to fill out and technical failures were encountered when using the sodium measurement device). These problems may have resulted in less (accurate) feedback on patients' sodium intake and goals, and thereby hampered the effectiveness of our intervention. Second, self-regulation theory considers behaviour change to be a goal process that can be divided into a motivational phase, an action phase, and a maintenance phase.[5] In the maintenance phase, interventions often include follow-up prompts (e.g., booster sessions, phone calls, postcards or emails)[46,64,65] to periodically refocus people's attention towards the goal, and to stimulate evaluation of the goal process, and the maintenance of the new behaviour(s). In our study, contact frequency was gradually reduced, but follow-up prompts were not included. The inclusion of follow-up prompts has been associated with increased effectivity,[58] and therefore, including an extended maintenance phase with follow-up prompts might result in maintenance of the low-sodium diet. Third, the biopsychosocial model considers the social domain to be important in health outcomes as well,[23] and, in line with this, previous studies also show that social support plays an important role in the initiation and maintenance of health behaviour change.[57,61] As suggested by literature, 'prompting social support' was included in our intervention and significant others were invited to attend meetings.[45,57,58] However, only 23 patients (34.3%) brought a significant other, usually their partner, to the meetings and social support among fellow patients was not facilitated. It is possible that an increased inclusion of significant others and/or the inclusion of group meetings with fellow patients might lead to increased intervention effects (e.g., educational low-sodium cooking sessions with fellow patients and partners[55]).

Environmental interventions

The results described in Chapters 2 and 3 also showed that patients perceive the high sodium content in products as the most important sodium reduction barrier and that patients believe that eating out is difficult when striving to adhere to a low-sodium diet. These findings may not come as a surprise given that 75 to 80% of our daily sodium intake comes from foods we buy (i.e., processed and catered foods).[66,67] Therefore, in order to adequately support patients with CKD in reducing their sodium intake, a broader biopsychosocial approach is imperative in which environmental interventions to reduce the sodium content in foods are implemented as well. Worldwide, such public health initiatives have been undertaken and these sodium reduction programs show promising results, however, there is still a lot of room for improvement.[68,69]

HRQOL and disease progression during predialysis care

Predialysis care aims to optimize disease control and HRQOL,[9,70] but the current treatment guidelines mainly seem to focus on clinical factors and outcomes, and less attention is paid to psychosocial factors and outcomes (e.g., illness perceptions and HRQOL).[9] A further integration of psychosocial aspects into the treatment guidelines would be an important next step for the implementation of biopsychosocial and patient-centred approaches into nephrological care, but in order for this to happen, additional research is required that provides evidence for the importance of psychosocial aspects in predialysis care. The results described in Chapters 5, 6 and 7 provide such evidence: these studies increase our knowledge about the course of HRQOL during predialysis care, and our knowledge about the importance of demographic, clinical *and* psychosocial factors with respect to disease progression *and* HRQOL of patients receiving predialysis care.

HRQOL during predialysis care

Increasingly, patients' HRQOL is seen as an important indicator of the effectiveness of medical care,[71,72] and therefore, knowledge about the development of HRQOL during predialysis care is indispensable. However, previous studies found contradictory results for the course of HRQOL during predialysis care (e.g., some studies found decreased mean levels of HRQOL[73–75] while others found no change in HRQOL[76,77]), and thus, it remained unclear how HRQOL evolved during predialysis care. The results described in Chapter 6 show that the contradictory findings may be explained by the heterogeneity of patients' evaluation of HRQOL during predialysis care. We identified three distinct physical HRQOL trajectories (i.e., a low-stable, medium-declining, and high-increasing trajectory – all containing approximately one-third of the sample) and two distinct mental HRQOL trajectories (i.e., a low-stable trajectory containing approximately two-third of the sample, and a high-stable trajectory containing approximately one-third of the sample). These results suggest that a large proportion of patients receiving predialysis care has an unfavourable (i.e., stable low or declining) HRQOL trajectory, which also puts them at risk for adverse outcomes (e.g., depression, accelerated progression towards ESKD and mortality).[73,78,79] Therefore, implementing patient-centred strategies into predialysis care to support patients at risk for impaired HRQOL is urgently needed.

Demographic/clinical factors and HRQOL

The results described in Chapters 5 and 6 showed that patients' evaluation of HRQOL during predialysis care differed depending on demographic and clinical patient characteristics. First, the findings in Chapter 6 suggest that the course of physical HRQOL may depend on patients' age and the presence of cardiovascular disease (CVD): increased odds for a low-stable physical HRQOL trajectory were detected in older patients and patients who also received the diagnosis CVD. Thus, these subgroups of patients may benefit most from additional support strategies to optimize HRQOL in predialysis care. Second, the findings in Chapter 5 also show that patients' evaluation of HRQOL differed depending on demographic and clinical factors, namely with regard to patients' age and Hb levels. The results show that high Hb levels (≥ 13 g/dL) by means of anaemia medication were associated with improved physical and mental HRQOL in young patients (< 65 years). However, in elderly (> 65 years), high Hb levels that were induced by anaemia medication were not associated with improved HRQOL – only natural high Hb levels were. These results suggest that there is a need for personalized treatment approaches to improve HRQOL during predialysis care and that these approaches should take into account age, Hb levels, and the presence of CVD.

Of these demographic and clinical factors, only Hb levels are modifiable and striving for higher Hb levels by means of anaemia medication has been identified as a treatment strategy to improve HRQOL.[10] However, striving for high Hb levels by means of anaemia medication could also increase the risks for adverse health outcomes (e.g., a cardiovascular events),[11] and therefore, the current treatment guidelines advise to strive for a narrow Hb target (≥ 11 to < 12 g/dL).[9,70] Scholars have argued that this 'one size fits all' approach to treat anaemia in patients with CKD does not seem appropriate and that patient characteristics such as age should be taken into account.[12,13,80] The results of Chapter 5 support this need for more individualised treatment plans: having high Hb levels by taking anaemia medication was associated with increased HRQOL in younger patients but not in elderly, and thus, suggests that the current anaemia treatment is optimal for elderly but not for younger patients. Overall, a patient-centred approach seems crucial with regard to the anaemia treatment: professionals and patients should discuss the potential individual benefits and risks of striving for higher Hb levels by means of anaemia treatment and together decide upon the most optimal Hb treatment target.

Illness perceptions, HRQOL and disease progression

Improving HRQOL solely via medication induced Hb levels may be insufficient because literature indicates that clinical factors are associated with HRQOL in patients with CKD, but also that, overall, clinical factors explain HRQOL only to a limited extent.[81–84] It is important to take a biopsychosocial and patient-centred approach seeing that, increasingly, studies show that psychosocial factors play an important role in understanding HRQOL of patients with CKD.[72, 84,85] For example, patients' beliefs about their illness – i.e., the self-regulation cognitions 'illness perceptions' – are major contributing factors to HRQOL in patients with ESKD.[17–21] The results described in Chapter 6 add to this knowledge by showing that stronger negative perceptions of illness are markers for unfavourable HRQOL trajectories during predialysis care, also after controlling for important demographic and clinical patient characteristics. Increased odds for an unfavourable HRQOL trajectory were detected in patients who attributed more physical symptoms to their kidney disease; believed to a higher extent that their kidney disease has an unpredictable cyclical nature, has negative consequences upon their lives, and causes emotional distress; and believed to a lesser extent that they can personally control their kidney disease and fully understand their kidney disease. Additionally, the findings in Chapter 6 suggest that, compared to the included demographic and clinical factors, illness perceptions are most closely related to HRQOL trajectories: only two out of eight demographic and clinical factors were associated with physical HRQOL trajectories (i.e., age and CVD) and no demographic or clinical factors were associated with mental HRQOL trajectories, while six out of eight illness perceptions were associated with physical HRQOL trajectories (i.e., illness identity, illness coherence, timeline cyclical, personal control, emotional response and negative consequences) and four out of eight illness perceptions were associated with mental HRQOL trajectories (i.e., illness coherence, timeline cyclical, emotional response and negative consequences). Furthermore, the results in Chapter 7 showed that stronger perceptions of timeline cyclical, negative consequences and emotional response, and weaker perceptions of personal control and illness coherence, were not only associated with unfavourable HRQOL trajectories (Chapter 6), but also with an accelerated disease progression during predialysis care (i.e., a faster kidney function decline and an earlier start of dialysis), also after controlling for a wide range of important demographic and clinical patient characteristics.

A possible explanation for the findings in Chapters 6 and 7 can be derived from Leventhal's Common Sense Model of self-regulation[32,33]: according to this self-regulation theory, illness perceptions guide the selection, adaption and maintenance of coping procedures – i.e., the "cognitive and behavioural actions we take (or do not take) to enhance health and to prevent, treat (i.e., cure or control), and rehabilitate from illness" (Leventhal, Leventhal, and Contrada, 1998, p. 772)[86] –, and consequently contribute to health outcomes. For our results, this could mean that patients with stronger negative perceptions of their illness deal with the kidney disease in more maladaptive ways (e.g., denial, not seeking support or nonadherence to treatment guidelines), and this results in unfavourable HRQOL trajectories and a faster disease progression. Unfortunately, measures for coping were not included in the PREPARE-2 dataset, and thus, it is not possible to explore this potentially mediating role of coping in the relationship between illness perceptions and outcomes. It is important to note that, so far, the evidence for this mechanism is inconsistent and mainly limited to cross-sectional studies[87]: for example, there are studies that found coping to mediate the relationship between illness perceptions and psychological well-being,[88] but there are also studies that found treatment adherence not to mediate the relationship between illness perceptions and clinical outcomes in patients with ESKD.[89]

The findings described in Chapters 6 and 7 underline the usefulness of a self-regulation and biopsychosocial approach as illness cognitions appear to be key factors with respect to both disease progression and HRQOL. These results are important for predialysis care, because – in contrast to many demographic and clinical factors that influence HRQOL and disease progression – illness perceptions are modifiable: self-regulation interventions aimed at changing illness perceptions resulted in better functional outcomes and an earlier return to work in patients recovering from a myocardial infarction,[15] and improved understanding of phosphate-binding medication and medication outcome efficacy beliefs among patients receiving haemodialysis treatment.[16] Identifying illness perceptions, for instance by means of the Brief Illness Perception Questionnaire,[90] may therefore provide opportunities to slow down disease progression and to optimize HRQOL in patients receiving predialysis care. Based upon patients' responses to the questionnaire, personalized treatment strategies can be provided and our results from

Chapters 6 and 7 suggest that key aspects of such strategies should be to target stronger perceptions of illness identity, timeline cyclical, negative consequences, and emotional response, and weaker perceptions of personal control and illness coherence. Examples of support strategies to target these unhelpful illness perceptions are: education (e.g., to target beliefs about illness coherence and personal control: enhance knowledge about the disease and treatment, and how they can personally influence disease progression by adopting a healthy lifestyle), identify and challenge misconceptions (e.g., to target beliefs about illness identity and timeline cyclical: discuss beliefs about the symptoms and course of CKD, and challenge incorrect attribution of symptoms to CKD and unrealistic expectations about the predictability and cyclical nature of CKD), and develop action plans (e.g., to target beliefs about personal control, emotional response, and negative consequences: plans about how to deal with emotional distress and the negative consequences of CKD upon their life, for instance by increasing social support or reattribution).[15,16,48,91] Until now, self-regulation interventions aimed at changing unhelpful illness perception have been developed for patients with ESKD[16,91,92] but, to the best our knowledge, no initiatives for developing and implementing interventions aimed to alter unhelpful illness perceptions in patients receiving predialysis care have been undertaken.

Strengths and limitations

Several considerations with regard to the strengths and limitations of the studies were offered in the corresponding chapters. In this section of the dissertation, more general considerations will be discussed.

Strengths

First, a main strength of this dissertation is that it provides in-depth knowledge about the daily experiences of patients with CKD and health care professionals with regard to sodium reduction (Chapters 2 and 3). By identifying (the importance of) a broad range of perceived sodium reduction barriers and potential support strategies, patient-centred approaches that fit the needs and preferences of patients and professionals can be developed and implemented into nephrological care.

Second, as far as we are aware, we designed and evaluated the first theory-based self-regulation intervention that encompassed multiple evidence-based behaviour change techniques[5,6,57–59] aimed at supporting patients in early stage CKD to incorporate the sodium treatment guidelines into their daily life (Chapter 4). Moreover, this behavioural approach was tailored according to the needs of patients and professionals (Chapter 2), and addressed the most important sodium reduction barriers and factors associated with experiencing barriers (i.e., self-efficacy and perceived autonomy support from professionals) (Chapter 3).

A third strength of this dissertation is that we used data from the prospective PREPARE-2 study that included a large sample (N = 502) of incident predialysis patients in the Netherlands (Chapters 5, 6 and 7). Due to the available repeated measurement in this observational study (i.e., at baseline and every six months thereafter), change over time could be investigated (i.e., HRQOL and kidney function) and clinical outcomes at the end of predialysis care could be included in the analysis (i.e., the start of dialysis).

Four, with the exception of Chapter 3, studies in this dissertation were multicentre studies: the studies from Chapters 2 and 4 included patients from four Dutch medical centres, and the studies from Chapters 5, 6 and 7 included patients from 25 Dutch medical centres. By using data of patients from multiple centres – both academic and non-academic centres –, we optimized the potential generalization of our results (i.e., the results represent the total CKD population in the Netherlands to a larger extent compared to single centre studies).

A fifth and final strength of this dissertation concerns the population of patients with CKD prior to ESKD. Previous research on sodium reduction and psychosocial aspects mainly focused on patients with ESKD, and this is understandable given the high disease burden in this final stage of the disease. However, it is important to expand our scope and also include the earlier stages of CKD during which there are still opportunities to delay the progression towards ESKD and prevent severely impaired HRQOL.

Limitations

Several limitations of the ESMO intervention study have already been mentioned in Chapter 4 and in the general discussion (e.g., problems with the self-monitoring tools). However, there are two additional limitations that should be mentioned. The first limitation pertains to the follow-up period: our randomised controlled trial did, in contrast to most sodium trials in patients with CKD,[51–55,93,94] report on the effectiveness *and* the sustainability of the sodium intervention, however, our follow-up period of six months (i.e., three months after the intervention period) could be considered brief. The inclusion of a longer follow-up period would have provided valuable information about long-term maintenance of our intervention effects and about effects on long-term renal and cardiovascular outcomes (e.g., clinical endpoints such as reaching ESKD, experiencing adverse cardiovascular events, and mortality). The second limitation concerns treatment fidelity of the therapists during the motivational interviews (i.e., do our coaches deliver the motivational interview in an adequate way). Literature suggests that characteristics of the interviews (i.e., the use of motivational interview skills, the motivational interview principles and 'spirit', etc.) influence the actual behaviour change,[40,95] and therefore, it is recommended that trials measure treatment integrity (e.g., by means of recording interviews and coding these recordings using Motivational Interviewing Treatment Integrity scales).[96,97] Our coaches – three health psychologists and one dietician – were all trained in the techniques of motivational interviewing, and based on the supervision of several interviews, we believe that our coaches were "motivational interview adherent". However, treatment fidelity was not assessed in our study, and therefore, it is impossible to provide evidence for the extent to which our therapists were "motivational interview adherent".

The relatively low response rates of the cross-sectional questionnaire-survey (Chapter 3) and the randomised controlled trial (Chapter 4) is also a limitation of this dissertation: in both studies the participation rate was approximately 50% (i.e., 59% and 45% for the cross-sectional study and trial, respectively). Although our response rates were similar to response rates that have been found in previous studies (e.g., 65% for postal questionnaire-surveys[98] and 47% for a trial evaluating a self-management intervention[99] in health care settings), it does limit the generalization of our results. Reasons to decline the study invitation were not available for the cross-sectional study, but were available for the trial and showed that the most common reasons were: poor health/wellbeing (14% of the refusals), no interest in the study (18%; e.g., too much work, too confronting or no need for a low-sodium diet), and the practical burden (39%; e.g., too much in combination with other obligations or too far a distance to travel). Unfortunately it was not possible to statistically explore differences between participants and non-participants, however, the reasons provided by non-participants suggest that there may be a selection bias in our trial sample (e.g., with regard to experienced health status or motivation to change sodium intake). With respect to the large group that indicated practical burden as a reason to not participate: for this subgroup, interventions comprising less face-to-face time and more e-health possibilities may be more suitable (e.g., less travelling, more flexibility to work on the program after working hours, etc.).

Another limitation of this dissertation is the possibility of confounding, a phenomenon in which the effects of the exposure (i.e., a risk factor or the independent variable) on the outcomes (i.e., the dependent variable) is mixed with the effects of another variable. For a variable to be considered a confounder, a variable needs to be related to both the exposure and the outcome (or disease), and not to be in the causal path between the exposure and the outcome.[100] Confounding is often encountered in studies that aim to investigate effects of an exposure on an outcome in an observational cohort study, and because confounders mask the real effect of an exposure on an outcome, it is important to remove the confounding effect as much as possible (e.g., by multivariate adjustments). In Chapters 5, 6, and 7 – the studies that used data of the observational PREPARE-2 cohort study, there were potential confounding effects. For example, a decreased health status (e.g., the presence of comorbidities) at the start of predialysis care could have caused stronger negative illness perceptions, and also more unfavourable HRQOL trajectories and a faster disease progression (Chapters 6 and 7). In all three chapters we aimed to get rid of possible confounding effects by extensive adjusting for potential confounders. However, it is difficult to define and measure all confounders, and thus, residual confounding may still have been present.

Furthermore, in this dissertation we included objective clinical measures but also subjective measures that were collected by means of self-report. Using self-report measures can have certain methodological downsides (e.g., the risk of response bias),[101,102] however, such issues can be partially avoided by using psychometrically sound questionnaires. The questionnaires used in this dissertation (i.e., Revised Illness Perception Questionnaire,[103] 36-item Short Form Health Survey,[104] Chronic Disease Self-Efficacy Scales - Manage Disease in General Scale,[105] Beck Depression Inventory,[106] Modified Health Care Climate Questionnaire,[107] and the Partner in Health questionnaire[108]), are considered psychometrically sound questionnaires and these questionnaires also showed good reliability in our studies (see Chapters 3, 4, 6 and 7). There is one exception, namely the questionnaire consisting of 18 self-formulated items to assess the importance of the perceived sodium reduction barriers in Chapter 3. However, we do not believe that using this unvalidated questionnaire led to biased results because this questionnaire showed moderate to good psychometric qualities in our study.

A final limitation is the missing data that we encountered in Chapters 3 to 7. Missing data could lead to biased results, with the extent of the bias depending on the amount of missing data, the type of missing data, and how missing data is handled. In brief, there are three categories of missing data: 'missing completely at random' (i.e., the probability that data 'Y' is missing does not depend on (un)known patient data, for example: HRQOL data is missing because some patients could not complete the questionnaire due to a broken pencil), 'missing at random' (i.e., the probability that data 'Y' is missing does not depend on 'Y', but may depend on known patient data, for example: HRQOL data is more often missing in younger patients, but in both younger and older patients missingness does not depend on the HRQOL values), and 'missing not at random' (i.e., the probability that data 'Y' is missing depends on 'Y' and unknown patient data, for example: HRQOL data is missing due to decreased HRQOL values caused by other reasons than the measured data).[109–111] We believe that in our studies the type of missing data was 'missing at random', which enabled us to use two state of the art methods to handle our missing data: 'maximum likelihood estimations' and 'multiple imputation'.[109–111] First, maximum likelihood estimations is a method in which missing data is not imputed or replaced, but handled within the statistical model by using all available data to compute maximum likelihood estimates of a parameter (i.e., the value of a parameter that is most likely to have resulted in the observed data).[110] Second, multiple imputation is a method in which plausible estimates of missing data are calculated based on known characteristics of each patient and this calculation is based on an imputation model (i.e., a prediction model that is created for the missing variable). This procedure is repeated for a number of times (e.g., 5 or 10 times) and results in multiple imputed datasets. To obtain the overall estimate and standard error of the imputed value, the estimates and standard errors in each imputation set are pooled.[109,111,112] These two methods are, contrary to more conventional methods (e.g., complete case analysis), recommended to ensure maximum power and to avoid bias estimates, and were used in this dissertation as follows:

- Maximum likelihood estimation was used to address all missing data in the latent class growth models and logistic regression models (Chapter 6), and to address missing outcomes in the linear mixed models (Chapters 4, 5 and 7).
- Multiple imputation was used to address all missing data in the correlation analysis (Chapter 3), and to address all missing baseline covariates or stratification variables in the linear mixed models to ensure the maintenance of power and the avoidance of bias *also* after adjustments and stratification (Chapters 4, 5 and 7; i.e., linear mixed models take into account missing outcomes by means of maximum likelihood estimations but not missing covariates).

There are some patients that were excluded from the analyses in Chapters 3 to 7 due to missing data, namely patients without any available data on the exposure or outcome. We excluded these patients because we believe that in these subgroups there was too little data to calculate reliable estimates for the missing data. Luckily, the various sensitivity analyses showed that little to no differences in patient characteristics were observed between patients who were included in and excluded from the analyses, which makes it less likely that thereby a selection bias was introduced.

Future directions for research and practice

Sodium reduction in early CKD

Taken together, the results of this dissertation show that patients in early stages of CKD face multiple important barriers when they try to adhere to the sodium treatment guidelines, especially patients with lower levels of self-efficacy. Implementing additional strategies into nephrological care is therefore urgently needed to provide patients with the support they need to successfully reduce their sodium intake and hereby contribute to slowing down disease progression.[3,4]

An important starting point for this support could be to identify and to address the sodium reduction barriers that patients experience, and the availability of a questionnaire to assess these sodium reduction barriers would be desirable. Such a questionnaire was developed within the context of this dissertation and this sodium reduction barrier questionnaire showed moderate to good psychometric qualities (Chapter 3). However, before this instrument can be used in nephrological care to identify sodium reduction barriers in individual patients with CKD, additional research is needed to further explore the reliability and validity of this questionnaire (e.g., the test-retest reliability: the consistency of the measurement over time when used among the same participants under the same conditions). Furthermore, additional research is needed to demonstrate whether changes in the extent to which patients experience sodium reduction barriers would also lead to changes in outcomes (e.g., sodium excretion, blood pressure or self-efficacy).

The results of this dissertation also suggest that a multicomponent patient-centred self-regulation intervention should be implemented into nephrological care. First, because such an intervention would fit the needs of patients and professionals (Chapters 2 and 3). Second, because such an intervention could result in various beneficial outcomes such as reduced risk factors for disease progression (e.g., blood pressure and protein excretion) and improved self-regulation cognitions (i.e., self-efficacy) in earlier stages of CKD (i.e., CKD stages 1 to 3) (Chapter 4). As described previously in the general discussion, it is possible that self-efficacy played a mediating role in our intervention effects, and additional research is therefore needed to investigate this suggested mechanism. Furthermore, the effects on the primary outcomes (i.e., sodium excretion and ambulatory blood pressures) waned over time, suggesting that the ESMO intervention needs to be improved before it can be implemented into nephrological care. The existing literature[6,55,57,58,61,65] and our experiences during the ESMO study (see previous description in the general discussion) suggest the following improvements: to include improved self-monitoring devices (i.e., a more robust sodium measurement device and a less complex online food diary); to include an extended maintenance phase with follow-up prompts (e.g., booster sessions); and to strengthening the social support (e.g., educational low-sodium cooking sessions with fellow patients and significant others). Future studies are needed to confirm whether these suggested improvements indeed lead to improved intervention effects.

A study that builds on the ESMO results and takes into account the suggested improvements, is the 'Sodium Burden lowered by Lifestyle Intervention: self-Management and E-health technology' (SUBLIME) study (ClinicalTrials.gov: NCT02132013). The SUBLIME study is also a multicentre randomised controlled trial in the Netherlands that evaluates the effectiveness of a multicomponent patient-centred self-regulation intervention aimed to support patients in early stages of CKD to reduce their sodium intake. Like the ESMO intervention, the SUBLIME intervention comprises education, feedback-consultations with a personal coach, self-monitoring of blood pressure, and self-monitoring of sodium intake by means of an online diary. Additionally, to take the limitations of the ESMO study into account *and* to create an intervention that is more suitable for cost-effective implementation into clinical care, the SUBLIME intervention did not include the sodium-measurement device (i.e., the device was expensive and not robust enough), but did include an improved version of the online food diary, two educational group meetings with fellow patients and significant others, online e-health modules based on motivational interview techniques (i.e., modules for goal setting, action and coping planning, choosing rewards, mobilizing social support, and relapse prevention), and an extended maintenance phase of six months with one or two follow-up moments with their coach (after an intervention phase of three months). The effectiveness of the SUBLIME intervention is currently evaluated.

Future intervention studies should also take psychological distress into account. Previous studies have shown that symptoms of depression and anxiety are very common in patients with CKD prior to ESKD,[113–115] and that psychological problems such as depressive symptoms are associated with nonadherence to treatment and poor clinical outcomes (e.g., hospitalization, faster disease progression and mortality).[61,113,114] The identification and treatment of psychological problems in early stages of CKD is therefore urgently needed, also to improve the extent to which patients are able to change their lifestyle habits such as sodium reduction. Currently, a screening tool and intervention for patients with CKD is developed to overcome psychological barriers to adopt a healthy lifestyle including sodium reduction and these tools will be evaluated in a multicentre randomised controlled trial in the Netherlands (the study 'Identifying and treating psychological barriers for adopting a healthy life style among patients with chronic kidney disease' [Dutch Kidney Foundation, SWO15.01]).

Furthermore, this dissertation suggests that environmental interventions could play an important role in the support of patients with CKD to reduce their sodium intake. In 2013, the World Health Organization also set the target to reduce the population's sodium intake with 30% by 2025 (i.e., toward 2000 milligrams sodium/5 grams salt per day).[116] Increasingly, countries also implement national sodium reduction strategies (e.g., improved nutrition labelling, consumer education, taxation on high-sodium foods or sodium targets for food manufacturers) and such strategies show promising results with regard to the population's salt intake, and also consumer knowledge about and attitudes towards sodium.[68,69] Since 2006, various initiatives have been taken in the Netherlands (e.g., a reduction of sodium in bread), and in 2014, the Dutch government and the food industry also came to an agreement that the sodium content of products would be reduced. Unfortunately, it seems that these initiatives and agreements have not yet translated into tangible reduction in sodium intake of the Dutch population.[117] Therefore, additional actions are required to reduce the sodium content in products (e.g., legally binding sodium targets for food manufacturers) and reduce the sodium intake of not only patients with CKD but the Dutch population in general.

Finally, until now, there are only limited multicomponent sodium interventions designed and evaluated among patients with CKD and none of these interventions used a full-factorial design. Therefore, little is known about the most optimal design for such interventions: which (combination of) behaviour change techniques should be included, what format works best (e.g., face-to-face, e-health, or blended; individual or group sessions), what is the most optimal duration and intensity for the intervention, etc. More research is therefore warranted and it is very important that future intervention studies report very clearly and transparent on the content of the intervention, including the use of the standardized method to report behaviour change techniques (e.g., the CALO-RE Taxonomy).[118] By standardized and clear reporting on the content, evidence about the effectiveness of sodium interventions can be synthesized and the most effective mix of ingredients can be identified (e.g., by means of systematic review and meta [regression] analysis).

HRQOL and disease progression during predialysis care

The results of this dissertation suggest that HRQOL remained compromised or became impaired in a large proportion of the patients during predialysis, and therefore, implementing support strategies aimed at improving HRQOL in this population is urgently needed. To identify patients in need for additional support, we recommend that professionals monitor HRQOL, for instance: regularly by means of the brief 12-item Short Form Survey or periodically with the more extensive 36-item Short Form Health Survey.[104,119] Moreover, the introduction of HRQOL measures – a measure that focuses on the patient rather the disease – into clinical care may also lead to increased patient-centredness of care (e.g., the introduction of HRQOL measures can be helpful to identify and prioritize primary concerns of the patient, facilitate communication regarding psychosocial problems and shared [clinical] decision making) and improved quality of care (e.g., the introduction of HRQOL measurements can be helpful to identify health care needs, and to measure disease progression and treatment response).[71,120]

According to our results, professionals should pay special attention to HRQOL in older patients and patients that received the diagnosis CVD, as these subgroups are at increased risk for impaired HRQOL trajectories. Another group of patients that deserves our attention are younger patients with anaemia; the results of this dissertation show that striving for high Hb levels (≥ 13 g/dL) by means of anaemia medication could improve HRQOL in younger but not elderly patients, suggesting that the current treatment guidelines (i.e., to strive for a narrow Hb target [≥ 11 to < 12 g/dL][9,70] because striving for high Hb levels could increase risks for negative health outcomes [e.g., cardiovascular events][11]) may not be optimal for younger patients. These findings underline the importance of individualised treatment approaches that take into account patient characteristics (e.g., age), and that include shared decision making (i.e., patients and professionals discuss possible positive and negative effects of the treatment, and together decide upon the most suitable treatment option for the individual patient). However, additional research is also warranted to explore whether the risks of striving for high Hb levels by means of anaemia medication (e.g., increased risk of experiencing a cardiovascular events), also differs between younger and elderly patients. Moreover, due to our observational design, causal interpretation is still limited, and therefore, randomised controlled trial are needed to investigate the causal relationship of targeting high Hb levels in the different age subgroups.

Furthermore, our results showed that patients with stronger negative perceptions of their kidney disease have an increased risk for impaired HRQOL and for a faster disease progression during predialysis care. These findings suggest that identifying illness perceptions in this population may create unique opportunities to improve outcomes, because unhelpful illness perceptions are modifiable by means of psychological interventions.[15,16] In nephrological care, it is therefore important that professionals identify patients' illness perceptions, for instance, with the Brief Illness Perception Questionnaire.[90] On the basis of patients' responses on the illness perception scales, illness perceptions can be discussed and, if needed, additional support should be provided (see previous description in the general discussion). However, future research is needed to increase our understanding of (the role of) illness perception and design effective self-regulation strategies aimed at changing unhelpful illness perception-based in this population. As a first direction for future research on illness perceptions: possible explanations for our findings in Chapters 6 and 7 should be explored. For example, the Common-Sense Model of self-regulation theory postulates that coping mediates the relationship between illness perceptions and outcomes,[32,33,86] and thus, future studies should investigate this potentially mediating role of coping in the relationship between illness perceptions, disease progression and HRQOL trajectories during predialysis care. Second, previous studies have shown that illness perceptions do not evolve only as a result of interventions that specifically target these perceptions, they also develop naturally over time[19,121]; change according to newly obtained knowledge and individual experiences[122]; and differ according to clinical status and medical treatment.[17,21,123] Until now, it is unclear how illness perceptions develop during the predialysis phase. It is possible that illness perceptions change during this intensive predialysis care (e.g., lead to weaker beliefs about personal or treatment control), and thereby indicate which additional support strategies aimed at changing negative illness perceptions could be of use to improve health outcomes during predialysis care. Three, the commonly-used Revised Illness Perception Questionnaire (IPQ-R) is a reliable and validated questionnaire, also among patients with ESKD.[103,124] However, possibilities to tailor the IPQ-R even better to the CKD population can be found in literature as well. For example, previous studies found a relatively low internal consistency for the domain 'treatment control' (i.e., the degree to which the patient believes that their kidney disease can be effectively managed by the treatment)[19,124] – possibly due to the use of "my treatment" in questions while many patients with CKD receive a multifaceted treatment due to comorbidities –, and the domain 'illness identity' (i.e., the symptoms that patients attribute to their kidney disease) could be tailored to the CKD-related symptoms even further.[125] Therefore, additional qualitative research is required to explore how the IPQ-R can be adapted in such way that it adequately captures the illness beliefs of patients receiving predialysis care (e.g., removal of items or adding disease-specific items). Four, the results from our studies (Chapters 6 and 7) are derived from observational studies, and thus, causal interpretation is limited. Randomised controlled trials are therefore needed to assess whether interventions aimed at modifying negative illness perceptions also lead to improved HRQOL trajectories, a slower decline of kidney function during predialysis care and a later start of dialysis.

Conclusions

This dissertation aimed to identify opportunities to slow down disease progression and improve HRQOL in patients with CKD prior to ESKD. Biopsychosocial, patient-centred and self-regulation perspectives were employed and enabled this dissertation to shed light on the importance of patients' health behaviours and illness perceptions in the treatment of CKD.

Taken together, this dissertation indicates that patients in early stages of CKD (i.e., CKD stages 1 to 3) are in need of additional behavioural support to cope with the broad range of barriers that they experience when reducing sodium intake. The results demonstrate that a multicomponent patient-centred self-regulation program would fit the needs of patients, and can reduce risk factors for disease progression and improve psychosocial outcomes (although some intervention effects did wane over time).

Furthermore, this dissertation suggests that additional support strategies should be implemented to increase the impaired HRQOL that many patients experience during predialysis care. The results underline the need for personalized treatment approaches in light of the differences between patients in relation to their HRQOL and how their HRQOL evolves over time (e.g., differences with regard to Hb levels, age, and CVD). Moreover, illness perceptions were found to be key factors in both HRQOL and disease progression, and therefore, treatment strategies in predialysis care should take into account patients' illness perceptions as well.

Despite limitations and the need for future research, we believe that we have taken important steps towards identifying opportunities to slow down disease progression and improve HRQOL in patients with CKD prior to ESKD. Finally, although the primary aim of this dissertation was not to test theoretical frameworks, it does support the need for biopsychosocial, patient-centred and self-regulation approaches in nephrological care.

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Nederlandse samenvatting (Summary in Dutch)

Inleiding

Een chronische nieraandoening is een ziekte waarbij de nierfunctie van mensen geleidelijk en blijvend afneemt. De ziekte kan worden onderverdeeld in vijf stadia van toenemende ernst, met stadium vijf als eindfase van de nierziekte, waarin een niervervangende behandeling (dialyse of transplantatie) nodig is om te overleven. Het aantal mensen dat met deze ziekte moet leven is de afgelopen jaren sterk toegenomen, en de verwachting is dat dit aantal de komende jaren nog verder zal toenemen door de vergrijzende populatie en toename in risicofactoren als overgewicht en diabetes.

Naarmate de nieraandoening zich verder ontwikkelt, neemt de impact van de ziekte op het leven van mensen en op de kosten van de gezondheidszorg toe. Strategieën om ziekteprogressie te vertragen in vroege fasen van de ziekte zijn daarom van groot belang. Het veranderen van gezondheidsgedrag speelt een belangrijke rol in het afremmen van ziekteprogressie, en in het bijzonder het eten van minder zout (natrium). Eerder onderzoek laat zien dat als het patiënten met een chronische nieraandoening lukt om de richtlijn van 5 gram zout (2000 mg natrium) per dag te halen, dit de gezondheid positief kan beïnvloeden (bijvoorbeeld: verlaging van de bloeddruk, verminderd risico op cardiovasculaire complicaties en bescherming van de resterende nierfunctie). Helaas lukt het de meeste patiënten met een chronische nieraandoening niet om de zout-richtlijn te halen, zelfs niet met hulp van zorgverleners. Aanvullende ondersteuning vanuit de zorg is dus nodig, maar om effectieve ondersteunings-strategieën voor deze groep patiënten te ontwikkelen is het belangrijk om te weten: welke barrières zij ervaren als ze proberen minder zout te eten, welke patiënten de meeste zoutvermindering-barrières ervaren, en welke strategieën het beste ingezet kunnen worden om patiënten te ondersteunen bij zoutvermindering. Eerder onderzoek laat zien dat multifactoriële programma's gericht op het bevorderen van zelfregulatie vaardigheden (bijvoorbeeld het stellen van concrete en haalbare doelen) en cognities (bijvoorbeeld het geloof in eigen kunnen), succesvol zijn in het veranderen van gezondheidsgedrag. Echter, tot op heden is niet onderzocht of dergelijke programma's ook effectief zijn in het helpen van patiënten in vroege fasen van de nierziekte bij zoutvermindering.

Voor patiënten in de predialyse fase – de fase waarin de ziekte al vergevorderd is, maar de patiënt (nog) geen niervervangende behandeling ontvangt – is het belangrijk om, in aanvulling op strategieën die ziekteprogressie vertragen, ook strategieën in te zetten om kwaliteit van leven zo hoog mogelijk te houden. Eerder onderzoek laat zien dat patiënten in de predialyse fase een verminderde kwaliteit van leven ervaren, maar er is nog weinig bekend over: hoe kwaliteit van leven zich gedurende de predialyse fase ontwikkelt, welke patiënten baat zouden hebben bij strategieën om kwaliteit van leven te verhogen, en welke strategieën het beste ingezet kunnen worden om kwaliteit van leven in deze groep te maximaliseren. Een potentiële medische strategie is om, door middel van medicatie, te streven naar hoge hemoglobine waarden in patiënten met bloedarmoede – een veelvoorkomende complicatie in deze fase van de nierziekte. Echter, het is nog onduidelijk wat de optimale hemoglobine streefwaarde is; eerder onderzoek laat zien dat hoge hemoglobine waarden door middel van medicatie inderdaad kwaliteit van leven kan verhogen, maar ook dat het risico's op negatieve gezondheidsuitkomsten (bijvoorbeeld cardiovasculaire complicaties) kan vergroten. Aanvullend onderzoek naar de relatie tussen hemoglobine waarden, bloedarmoede medicatie en kwaliteit van leven is daarom nodig voordat deze strategie ingezet kan worden in de zorg. Mogelijkheden om kwaliteit van leven met niet-farmaceutische strategieën te verhogen moeten ook worden onderzocht. Eerdere studies concludeerden dat de gedachten die mensen over hun ziekte hebben (ziektepercepties) een belangrijke rol spelen in hoe zij met hun ziekte omgaan en hoe het met hen gaat. Ook laat onderzoek zien dat ongunstige ziektepercepties veranderd kunnen worden door middel van psychosociale ondersteuningsstrategieën en dat de gezondheid hierdoor verbetert. Echter, tot op heden is weinig bekend over de rol die ziektepercepties spelen in zowel kwaliteit van leven als ziekteprogressie van patiënten die predialyse zorg ontvangen.

Het bovenstaande laat zien dat er nog belangrijke stappen te nemen zijn om ziekteprogressie af te remmen en kwaliteit van leven te maximaliseren in patiënten met een chronische nieraandoening voordat ze niervervangende behandeling ontvangen. Dit proefschrift richt zich op het identificeren van mogelijkheden om de zorg voor deze groep patiënten te verbeteren door gebruik te maken van een biopsychosociaal, patiëntgericht en zelfregulatie perspectief.

Biopsychosociaal perspectief

Het biopsychosociaal model werd in 1977 geïntroduceerd door George L. Engel om geneeskunde aan te moedigen om de beperkte biomedische benadering van gezondheid en ziekte uit te breiden.[1] Het model stelt voor dat, om de gezondheid van patiënten te verbeteren, artsen niet alleen aandacht moeten hebben voor de biomedische aspecten van ziekte, maar ook voor de psychologische en sociale aspecten. Deze meer holistische aanpak van geneeskunde waarin de subjectieve ervaring en het gedrag van patiënten centraal staat, wordt wereldwijd gesteund en omarmd.

Patiëntgericht perspectief

Patiëntgerichte zorg kan worden omschreven als "zorg georganiseerd rondom de patiënt [...] waarin zorgverleners samenwerken met de patiënt en hun familie om alle behoeften en voorkeuren van de patiënt te identificeren en hierin te voorzien" (Frampton et al., 2008, p. 4).[2] Veel patiënten verlangen patiëntgerichte zorg, en om zulke zorg te geven, is het onder andere belangrijk dat zorgverleners een biopsychosociale aanpak hanteren, navraag doen naar de behoeften en zorgen van patiënten, aandacht besteden aan gezondheidsbevordering, en dat patiënten en zorgverleners gezamenlijk beslissen over het behandelplan en zij een goede relatie hebben.

Zelfregulatie perspectief

Zelfregulatie kan worden omschreven als "een systematisch proces van menselijk gedrag met betrekking tot het stellen van persoonlijke doelen en de aansturingprocessen om de gestelde doelen te bereiken" (Zeidner, Boekaerts and Pintrich, 2000, p. 751).[3] Dit dynamisch proces kan worden onderverdeeld in drie fasen: a) een motivatiefase (een fase van doelselectie), een actiefase (een fase waarin het doel actief wordt nagestreefd), en een volhoudfase (een fase waarin het doel wordt bereikt, behouden of losgelaten). Om deze fasen te doorlopen, en zo gedrag succesvol te veranderen, zijn verschillende zelfregulatie vaardigheden (bijvoorbeeld het monitoren van gedrag) en cognities (bijvoorbeeld ziektepercepties) van belang. Zelfregulatie theorie is een vaak gebruikt psychologisch kader om gezondheidsgedrag te begrijpen en waar vanuit ondersteuningsstrategieën kunnen worden afgeleid.

Deze drie gerelateerde perspectieven zijn in dit proefschrift onder andere toegepast door voortdurend de relatie tussen demografische, medische en psychosociale factoren en uitkomsten te analyseren; de ervaringen en behoeften van patiënten te identificeren; de rol van ziektepercepties in kwaliteit van leven en ziekteprogressie te onderzoeken; mogelijkheden voor geïndividualiseerde behandelingen te verkennen; en patiëntgerichte zelfregulatie strategieën voor leefstijlverandering te evalueren.

Studies in dit proefschrift: belangrijkste bevindingen, implicaties en vervolgonderzoek

Deel een: zoutvermindering in vroege fasen van de nierziekte

In **hoofdstuk 2** wordt een kwalitatieve studie beschreven waarin is onderzocht welke barrières patiënten met een chronische nieraandoening ervaren als ze minder zout proberen te eten en aan welke ondersteuning zij behoefte hebben. Er zijn acht groepsgesprekken met patiënten en zorgverleners uit vier Nederlandse ziekenhuizen gehouden (25 patiënten en 23 zorgverleners in totaal). Uit deze gesprekken bleek dat de meeste patiënten proberen minder zout te eten, maar dat zij het moeilijk vinden om dit op de langere termijn vol te houden of om het advies volledig op te volgen. Dat patiënten te veel zout blijven eten, komt door uiteenlopende barrières die goed passen binnen het kader van zelfregulatie theorie. Zo lijken patiënten bijvoorbeeld een sterke persoonlijke motivatie voor zoutvermindering te missen, nog geen nierziekte-gerelateerde symptomen te ervaren, een negatieve houding ten aanzien van zoutvermindering te hebben (bijvoorbeeld dat zoutarm eten vies, duur en ongezellig is), over onvoldoende kennis te beschikken (met name praktische kennis over hoe je minder zout kan eten), geen persoonlijke zoutdoelen te stellen en geen zoutvermindering-strategieën met zorgverleners te bespreken, vaardigheden te missen (bijvoorbeeld hoe ga je om met eten in sociale situaties), een gebrek aan feedback op zoutinname te ervaren, en te weinig patiëntgerichte ondersteuning van zorgverleners te krijgen. Ook gaven patiënten aan dat het hoge zoutgehalte in voeding een belangrijke barrière is. Tot slot, werd een breed scala aan ondersteuningsstrategieën als belangrijk gezien, bijvoorbeeld: het zelfmeten van zoutinname, educatie over voeding en feedback van een coach.

Hoofdstuk 3 beschrijft een kwantitatieve cross-sectionele studie waarin is onderzocht hoe belangrijk de geïdentificeerde zoutvermindering-barrières (hoofdstuk 2) werden gevonden door een bredere populatie van patiënten met een chronische nieraandoening, en welke patiënten de meeste barrières ervaren op basis van demografische, medische en psychosociale karakteristieken. Voor dit onderzoek werd een zoutvermindering-barrière vragenlijst ontwikkeld en zijn gegevens gebruikt van 156 patiënten uit een Nederlands ziekenhuis die de vragenlijst volledig hadden ingevuld. De resultaten lieten zien dat de geïdentificeerde zoutvermindering-barrières ook door een bredere populatie als belangrijk werden ervaren. De volgende barrières werden als zeer belangrijk gezien: het hoge zoutgehalte in voeding, geen persoonlijke zoutdoelen stellen en zoutvermindering-strategieën bespreken, te weinig feedback op zoutinname ontvangen en geen nierziekte-gerelateerde symptomen ervaren. De overige barrières (een negatieve houding ten aanzien van een zoutarm dieet, en een gebrek aan vaardigheden in sociale situaties, patiëntgerichte steun van zorgverleners en kennis) werden als belangrijk ervaren, en persoonlijke motivatie werd als een matig belangrijke barrière gezien. Verschillende patiëntkarakteristieken hingen samen met het ervaren van zoutvermindering-barrières, namelijk leeftijd, opleidingsniveau, comorbiditeit (diabetes en/of hart- en vaatziekten), depressieve symptomen, ervaren autonomie-ondersteuning van zorgverleners, en zelfeffectiviteit (geloof in eigen kunnen). Ten slotte bleken zelfeffectiviteit en ervaren autonomie-ondersteuning van zorgverleners – twee belangrijke factoren in zelfregulatie theorie –, samen te hangen met de hoeveelheid zoutvermindering-barrières die patiënten ervoeren: de meeste problemen met zoutvermindering werden ervaren door patiënten die in een mindere mate geloofden dat zij in staat waren om goed met de ziekte om te gaan en in een mindere mate geloofden dat zij voldoende autonomie-ondersteuning van zorgverleners te ontvangen.

In **hoofdstuk** 4 wordt de Effects of Self-Monitoring on Outcome of Chronic Kidney Disease (ESMO) interventie studie beschreven, waarin is onderzocht of een patiëntgericht zelfregulatie programma in staat is om patiënten met een chronische nieraandoening goed te ondersteunen bij zoutvermindering en hun gezondheid te verbeteren. Het programma werd in samenspraak met patiënten en zorgverleners ontwikkeld, is gericht op veel van de belangrijke barrières en factoren voor zoutvermindering (hoofdstuk 2 en 3), en is geëvalueerd met behulp van 151 patiënten uit vier Nederlandse ziekenhuizen. De patiënten in de controle groep kregen alleen de standaardzorg, en patiënten uit de interventie groep kregen de standaardzorg en het programma dat bestond uit: educatie, een niervriendelijk kookboek, verschillende vormen van zelfmonitoren (het thuis meten van bloeddruk, van natriuminname met behulp van een online voedingsdagboek en van het natriumgehalte in de urine met speciale lab-on-a-chip techniek), coaching per telefoon en twee individuele motiverende gesprekken (onder andere gericht op het versterken van intrinsieke motivatie en zelfeffectiviteit, het formuleren van persoonlijke, concrete zoutdoelen en zoutreductie actieplannen, het bespreken van zoutvermindering-barrières en oplossingen, evaluatie en terugvalpreventie). De resultaten lieten zien dat het programma, vergeleken met de reguliere zorg, een gunstig effect had op natrium- en eiwitgehalte in de urine, bloeddruk, gewicht en zelfeffectiviteit direct na de interventie van drie maanden. Na zes maanden leken de effecten van het programma op natrium te zijn afgezwakt, maar bleven de positieve effecten op eiwit in de urine, bloeddruk, gewicht en zelfeffectiviteit bestaan. Bovendien werd het programma zeer positief beoordeeld door patiënten, ondanks dat er problemen waren met het zelfmeten van natrium (de innovatieve natriummeter gaf soms foutmeldingen en het voedingsdagboek was complex om in te vullen).

Uit de resultaten van het eerste deel van dit proefschrift blijkt dat patiënten veel belangrijke barrières ervaren als ze minder zout proberen te eten, met name patiënten met minder zelfeffectiviteit en autonomie-ondersteuning. Ze hebben behoefte aan extra steun vanuit de zorg en er lijkt geen 'one size fits all' benadering mogelijk om patiënten goed te ondersteunen bij het starten en volhouden van een zoutarm dieet. Een ondersteuningsstrategie die goed aansluit bij de behoefte van patiënten is een multifactoriële patiëntgerichte strategie waarin gezamenlijke besluitvorming en coaching centraal staan, verschillende individuele barrières worden geadresseerd, en zelfeffectiviteit en autonomie worden versterkt. In dit proefschrift is een belangrijke eerste stap gezet met het aanbieden van dergelijke ondersteuning, en uit de resultaten blijkt dat zo'n programma ook in staat is om belangrijke gezondheidsuitkomsten voor patiënten met een chronische nieraandoening te verbeteren. Verder onderstreept dit proefschrift ook de noodzaak voor maatschappelijke initiatieven om het hoge zoutgehalte in voeding te verlagen.

Een aanbeveling voor de praktijk is om de zoutvermindering-barrières van patiënten te identificeren en te bespreken. De ontwikkelde zoutvermindering-barrière vragenlijst zou hier een belangrijke rol in kunnen spelen. Echter, voordat de vragenlijst in de nefrologische zorg kan worden ingezet om barrières van individuele patiënten te identificeren, is vervolgonderzoek naar de betrouwbaarheid en validiteit van de vragenlijst nodig. Verder onderzoek is ook noodzakelijk om na te gaan of veranderingen in de mate waarin patiënten zoutvermindering-barrières ervaren, ook leiden tot veranderingen in gezondheidsuitkomsten. Het ontwikkelde ondersteuningsprogramma zal, voordat het ingezet kan worden in de nefrologische zorg, verder verbeterd moeten worden en suggesties voor verbeteringen zijn: versterken van sociale steun (bijvoorbeeld groepsbijeenkomsten), verbeterde zelfmonitoringshulpmiddelen (een minder complex voedingsdagboek en een verbeterde natriummeter) en een volhoudmodule (bijvoorbeeld extra feedbackmomenten na de actieve interventieperiode). Andere belangrijke vervolgstappen zijn om het programma kosteneffectiever te maken (bijvoorbeeld goedkopere technologie voor zelfmonitoring) en om in het programma meer aandacht te besteden aan de rol van psychologische barrières voor gedragsverandering (bijvoorbeeld depressieve symptomen).

Deel twee: ziekteprogressie en kwaliteit van leven in de predialyse fase

In het tweede deel van dit proefschrift wordt gebruik gemaakt van data uit een observationele studie, de PREdialysis PAtient REecord-2 (PREPARE-2) studie. Aan deze studie nemen 502 patiënten deel uit 25 Nederlandse nierfalen poliklinieken. Tijdens de studie ontvangen deelnemers de gebruikelijke zorg, en deelnemers worden gevolgd tot ze een niertransplantatie ondergaan, starten met dialyse, overlijden of een andere studie-gerelateerde uitkomst. Demografische, medische en psychosociale gegevens zijn verzameld aan het begin van de studie en elke zes maanden daarna.

Hoofdstuk 5 beschrijft een studie waarin is onderzocht wat de gecombineerde relatie is van hemoglobine waarden en het gebruik van bloedarmoede medicatie (erytropoëtine stimulerende middelen/ijzer preparaten) op kwaliteit van leven gedurende de eerste twee jaar van de predialyse zorg, en of deze relatie verschilt voor jongere (jonger dan 65 jaar) of oudere (65 jaar of ouder) patiënten. Voor deze studie is gebruikt gemaakt van gegevens van 371 patiënten uit de PREPARE-2 studie, en de resultaten lieten zien dat de relatie tussen hemoglobine waarden en kwaliteit van leven verschilt per leeftijdscategorie en het gebruik van medicatie. Zo rapporteerden oudere patiënten met natuurlijk hoge hemoglobine waarden (dus zonder medicatie) een betere fysieke en mentale kwaliteit van leven vergeleken met oudere patiënten met normale hemoglobine waarden (zoals geadviseerd in de huidige behandelrichtlijn). Echter, deze relatie tussen hoge hemoglobine waarden en een betere kwaliteit van leven werd niet gevonden in oudere patiënten die medicatie kregen voorgeschreven. Jongere patiënten met hoge hemoglobine waarden rapporteerden ook een betere fysieke en mentale kwaliteit van leven, maar dit betrof alleen patiënten die juist wel medicatie kregen voorgeschreven. Deze bevindingen laten zien dat het streven naar hoge hemoglobine waarden door middel van medicatie inderdaad kwaliteit van leven kan verhogen, maar alleen in jongere patiënten die predialyse zorg ontvangen.

In **hoofdstuk 6** wordt een studie beschreven waarin is onderzocht of er verschillende kwaliteit van leven trajecten kunnen worden geïdentificeerd gedurende de eerste 18 maanden van de predialyse zorg, en of deze trajecten verschillen op basis van demografische karakteristieken, medische karakteristieken en ziektepercepties aan de start van de predialyse zorg. Voor dit onderzoek is gebruik gemaakt van gegevens van 396 patiënten uit de PREPARE-2 studie, en de resultaten lieten zien dat patiënten verschillen in hoe zij kwaliteit van leven gedurende de predialyse zorg evalueren. Drie fysieke kwaliteit van leven trajecten werden geïdentificeerd, elk bestaande uit ongeveer een derde van de studiepopulatie: een traject waarin patiënten een stabiel lage fysieke kwaliteit van leven rapporteerden, een traject waarin patiënten hun fysieke kwaliteit van leven evalueerden als middelmatig en die over tijd afnam, en een traject waarin patiënten een hoge fysieke kwaliteit van leven rapporteerden die over tijd verder toenam. Twee mentale kwaliteit van leven trajecten werden geïdentificeerd: een derde van de studiepopulatie evalueerde hun mentale kwaliteit van leven als stabiel hoog, en twee derde gaf aan een stabiel lage mentale kwaliteit van leven te ervaren. Ook bleken er verschillende factoren samen te hangen met de kans op een ongunstige (stabiel lage of afnemende) kwaliteit van leven traject: een grotere kans op een ongunstig fysieke kwaliteit van leven traject werd gevonden in oudere patiënten en patiënten met hart- en vaatziekten, en een grotere kans op het ervaren van een ongunstig fysieke en mentale kwaliteit van leven traject werd gevonden in mensen die meer symptomen toewijzen aan hun nierziekte, in mensen die sterker geloofden dat hun nierziekte onvoorspelbaar en cyclisch van aard was, veel negatieve consequenties had, en veel negatieve gevoelens veroorzaakte, en in mensen die sterker geloofden dat ze hun nierziekte niet helemaal begrepen en er geen persoonlijke controle over hadden. Deze resultaten tonen aan dat de meerderheid van de patiënten tijdens de predialyse zorg een ongunstig kwaliteit van leven traject ervaren, en dat leeftijd, hart- en vaatziekten en ziektepercepties een belangrijke rol spelen in hoe kwaliteit van leven zich ontwikkelt gedurende de predialyse zorg.

Hoofdstuk 7 beschrijft een studie waarin is onderzocht of ziektepercepties aan de start van de predialyse zorg ook samenhingen met ziekteprogressie gedurende de predialyse zorg (gemeten als de achteruitgang van nierfunctie over tijd en de tijd tot aan het starten met dialyseren). Voor dit onderzoek zijn de gegevens van 416 patiënten uit de PREPARE-2 studie gebruikt, en de resultaten lieten zien dat sterkere negatieve ziektepercepties samenhingen met een snellere ziekteprogressie tijdens de predialyse zorg: de nierfunctie ging sneller achteruit en dialyse werd eerder gestart in patiënten die sterker geloofden dat hun nierziekte onvoorspelbaar en cyclisch van aard was, veel negatieve consequenties had en veel negatieve gevoelens veroorzaakte. Ook ging de nierfunctie sneller achteruit in patiënten die sterker geloofden dat ze hun nierziekte niet helemaal volledig begrepen en er geen persoonlijke controle over hadden.

De resultaten uit het tweede deel van dit proefschrift tonen aan dat veel patiënten een verminderde kwaliteit van leven ervaren, en dat aanvullende ondersteuning nodig is om kwaliteit van leven in de predialyse zorg te verhogen. Een aanbeveling is dan ook om kwaliteit van leven met een korte vragenlijst (bijvoorbeeld de 12-item Short-Form Survey) te meten om zo patiënten met een verminderde kwaliteit van leven te identificeren. Uit de resultaten van dit proefschrift blijkt ook dat zorgverleners extra aandacht moeten besteden aan oudere patiënten en patiënten met hart- en vaatziekten, omdat zij een verhoogd risico lopen op een ongunstig kwaliteit van leven traject tijdens de predialyse zorg. Jongere patiënten met bloedarmoede verdienen ook extra aandacht aangezien kwaliteit van leven in deze subgroep verhoogd kan worden door het streven naar hoge hemoglobine waarden door middel van bloedarmoede medicatie. Al deze resultaten illustreren de noodzaak van patiëntgerichte zorg waarin de behandeling wordt afgestemd op patiëntkarakteristieken (bijvoorbeeld leeftijd) en er gezamenlijke besluitvorming plaatsvindt waarin de wensen van de patiënt centraal staan (bijvoorbeeld zorgverleners en patiënten maken gezamenlijk de balans op van mogelijke voor- en nadelen van hoge hemoglobine waarden door middel van medicatie). Gezien het observationele ontwerp van de PREPARE-2 studie, is het wel aan te bevelen dat een gerandomiseerde studie wordt uitgevoerd om de causale relatie tussen de effecten van hoge hemoglobine waarden in verschillende leeftijdsgroepen te onderzoeken.

De resultaten van dit proefschrift tonen ook aan dat ziektepercepties een goed aanknopingspunt kunnen zijn voor de behandeling van patiënten in de predialyse zorg: sterkere negatieve ziektepercepties hangen samen met een snellere ziekteprogressie, en een ongunstig fysiek en mentaal kwaliteit van leven traject. Aanbevelingen voor de praktijk zijn om ongunstige ziektepercepties vroegtijdig te identificeren (bijvoorbeeld door gebruik te maken van de Brief Illness Perception Questionnaire), te bespreken, en, indien nodig, aanvullende psychosociale ondersteuning aan te bieden. Hiermee wordt niet alleen de beleving van de patiënt centraal gesteld, maar kan mogelijk ook kwaliteit van leven en ziekteprogressie positief worden beïnvloed. Meer en verder onderzoek op dit gebied is noodzakelijk, bijvoorbeeld: een kwalitatief onderzoek om de ziekteperceptie vragenlijst beter af te stemmen op de beleving van nierpatiënten, een studie om de gevonden relaties tussen ziektepercepties en uitkomsten te verklaren (coping medieert mogelijk de relatie tussen ziektepercepties en uitkomsten), en een interventie studie om te onderzoeken of een programma gericht op het veranderen van ongunstige ziektepercepties ook daadwerkelijk leidt tot betere gezondheidsuitkomsten in de predialyse zorg.

Conclusie

Het doel van dit proefschrift was om mogelijkheden te identificeren om ziekteprogressie te vertragen en kwaliteit van leven te verbeteren in patiënten met een chronische nieraandoening voordat ze niervervangende behandeling ontvangen. De biopsychosociale, patiëntgerichte, en zelfregulatie perspectieven werden toegepast om licht te schijnen op de rol van gezondheidsgedrag en ziektepercepties in patiënten met een chronische nieraandoening.

Dit proefschrift toont aan dat patiënten in vroege fasen van de nierziekte behoefte hebben aan extra gedragsmatige ondersteuning vanuit de zorg om met de diverse belangrijke zoutvermindering-barrières om te gaan. Ook werd aangetoond dat een multifactorieel patiëntgericht zelfregulatie programma aan de behoeften van patiënten voldoet en in staat is om belangrijke risicofactoren voor ziekteprogressie en psychosociale uitkomsten te verbeteren (al vlakte sommige effecten af over tijd).

Uit dit proefschrift blijkt ook dat aanvullende ondersteuning nodig is om de aangetaste kwaliteit van leven van patiënten tijdens de predialyse zorg te verbeteren. Het belang van gepersonaliseerde ondersteuning werd onderstreept door de gevonden verschillen tussen patiënten als het gaat om (de ontwikkeling van) kwaliteit van leven, bijvoorbeeld verschillen in hemoglobine waarden, leeftijd, en het hebben van hart- en vaatziekten. Bovendien bleken ziektepercepties een belangrijke rol te spelen in zowel kwaliteit van leven als ziekteprogressie gedurende de predialyse zorg, en het is daarom belangrijk dat ondersteuningsstrategieën ook inspelen op ziektepercepties van patiënten.

Ondanks de beperkingen van de uitgevoerde studies en de noodzaak voor vervolgonderzoek, heeft dit proefschrift een belangrijke stap gezet in het identificeren van mogelijkheden om ziekteprogressie te vertragen en kwaliteit van leven van patiënten met een chronische nieraandoening te verbeteren. Als laatste onderschrijft dit proefschrift ook, ondanks dat het toetsen van theoretische kaders niet het primaire doel van dit proefschrift was, het belang van een biopsychosociale, patiëntgerichte en zelfregulatie benadering in de nefrologische zorg.

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Curriculum vitae

Yvette Meuleman was born on 11 September 1982 in The Hague, the Netherlands. After finishing her secondary education in 2001 at the Maerlant Lyceum in The Hague, she worked and travelled before starting her Bachelors in Psychology at Leiden University. In 2009, she graduated cum laude in the Master Health Psychology at Leiden University with a thesis on self-regulation in post-cardiac rehabilitation patients and an extended (research and practical) internship under supervision of dr. Veronica Janssen. During her Masters she started working as a research assistant at the Clinical and Health Psychology department of Leiden University, which she continued for one year after graduation.

In 2009, she started her PhD project at the Medical Psychology department of Leiden University Medical Centre. During her PhD she was involved in various research initiatives regarding lifestyle and psychosocial aspects in patients with chronic kidney disease (e.g., co-founder of the working group ‘Self-management in Nephrology the Netherlands’ and co-designer of psychological behaviour change e-health modules), reviewed manuscripts for psychological and nephrological scientific journals, and gave presentations at numerous (inter)national conferences. In 2015-16, she was employed as a researcher at the Health, Medical, and Neuropsychology of Leiden University on the project ‘Who takes care of the caregivers: risk profiles for overburden in informal caretakers?’ under supervision of dr. Winnie Gebhardt. Since 2008, she has also provided lifestyle and stress management counselling for cardiac patients and patients with chronic kidney disease, and taught health care professionals in the techniques of motivational interviewing.

Yvette started teaching at Leiden University in 2008; first, at the department of Clinical and Health Psychology, and since 2014, at the department of Health, Medical, and Neuropsychology. Over the years, she taught Bachelor and Master courses to Dutch and international psychology students regarding health and medical psychology (e.g., health promotion and disease prevention, basic therapeutic skills, and psychological assessment and interventions in chronic disease), mentored students and supervised Master thesis students. Additionally, she taught health and medical psychology courses to medical Bachelor students at Leiden University Medical Centre and mentored medical interns with regard to communication and professionalism.

Currently, Yvette holds a teaching position at the department of Health, Medical, and Neuropsychology of Leiden University.