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**LIVING WITH CHRONIC  
KIDNEY DISEASE –  
PERCEPTIONS OF ILLNESS  
AND HEALTH-RELATED  
QUALITY OF LIFE**

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*Det finns mitt i skogen en oväntad glänta som bara kan hittas av den som gått vilse. Gläntan är omsluten av en skog som kväver sig själv. Svarta stammar med lavarnas askgrå skäggstubb. De tätt sammanskruvade träden är döda ända upp i topparna där några enstaka gröna kvistar vidrör ljuset. Därunder: skugga som ruvar på skugga, kärret som växer. Men på den öppna platsen är gräset underligt grönt och levande. Här ligger stora stenar, liksom ordnade. De måste vara grundstenarna i ett hus, jag kanske tar fel...*

Ur 'Gläntan' av Tomas Tranströmer

## ABSTRACT

This thesis comprises two studies concerning illness perceptions and perceived health-related quality of life (HRQoL) in patients with chronic kidney disease (CKD). The overall aim was to evaluate psychometric properties of a Swedish translation of the Revised Illness Perception Questionnaire (IPQ-R) (study I), and furthermore to explore illness perceptions (study I) and HRQoL (study II) in adult patients in different stages of renal insufficiency (CKD stages 2-5). In **study I**, evidence for construct validity was gathered through cognitive interviews (N=7) and other psychometric assessments (n=54). The results supported construct validity of the IPQ-R in a CKD context. The most supported IPQ-R dimensions were identity, timeline cyclical, consequences and emotional representations. The illness coherence, timeline and controllability dimensions need to be further explored in this patient group. Most IPQ-R dimensions distinguished illness perceptions between groups of different CKD stages and symptom burden. The patients in earlier CKD stages (CKD stages 2-3) or with <8 symptoms did not hold as strong beliefs about their illness being as threatening as those in the advanced stages (CKD stages 4-5) or with  $\geq 8$  symptoms. The patients who experienced more symptoms or had more advanced CKD expressed less illness coherence than those experiencing fewer symptoms or in earlier CKD stages. Negative illness perceptions, i.e. experiencing more symptoms and perceiving the illness as more threatening was associated with an impaired HRQoL and also with mainly evasive, fatalistic, emotive and supportant coping styles. A substantial part of the patient responses referred to behavioural and psychological attributions as contributory causes to their CKD. Leg cramps, stiff/sore joints, dry skin and impaired sexual desire/ability were the most commonly reported symptoms in earlier CKD stages. Fatigue, lack of energy, leg cramps and thirst were the most common symptoms in the advanced disease stages. An uncertainty assessing symptoms attributed to CKD was indicated, especially in earlier CKD stages. **Study II** had a cross-sectional design with 535 patients across different stages of renal insufficiency (CKD stages 2–5) up to initiation of dialysis treatment, and 55 controls assessed for HRQoL through the SF-36 questionnaire together with biomarkers. All HRQoL dimensions deteriorated significantly with impaired kidney function, with the lowest scores in those with kidney failure (CKD 5). The largest differences between the patient groups were seen within physical health. The smallest disparities were seen in bodily pain and mental health. Patients in earlier CKD stages showed significantly decreased HRQoL compared to matched controls. Patients in CKD 5 demonstrated significantly deteriorated scores also in mental health compared to those in CKD 4. Glomerular filtration rate  $<45$  ml/min/1.73 m<sup>2</sup>, age  $\geq 61$  years, cardiovascular disease (CVD), diabetes, C-reactive protein (CRP)  $\geq 5$  mg/L, haemoglobin  $\leq 110$  g/L, p-albumin  $\leq 35$  g/L and overweight were associated with impaired HRQoL. CRP and CVD emerged as primary predictors of impaired HRQoL, followed by reduced GFR and diabetes.

In renal care, increased understanding of illness perceptions and HRQoL are important assignments, since they interrelate and also have an impact on the patients' coping and health behaviour. Skilled attention to the patients' illness perceptions and HRQoL may enable health care providers to identify patients at risk for sub-optimal self-management and/or impaired HRQoL, identify and focus on relevant problems as well as supporting healthy behaviour, self-management and self-care. There is a need to further evaluate effective strategies to enhance illness perceptions and HRQoL in CKD patients such as educational interventions, programmes for improved physical activity and - especially in advanced CKD - proper psychosocial support. The findings also indicate that renal care may benefit from a more comprehensive approach, including increased attention to health promoting interventions regarding risk factors and comorbid conditions.

**Keywords:** Chronic kidney disease, illness perceptions/representations, Health-related quality of life, health behaviour, self-management, nursing, comorbidity.

## LIST OF PUBLICATIONS

- I. Evaluating the illness perception questionnaire on patients with chronic kidney disease in Sweden.  
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- II. Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment.  
**Pagels A A**, Klang Söderkvist B, Medin B, Hylander B, Heiwe S. *Health and Quality of Life Outcomes* 2012, Jun 18;10(1):71. [Epub ahead of print] PMID: 22710013

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## LIST OF ABBREVIATIONS

BMI	Body Mass Index (kg/m <sup>2</sup> )
BP	Bodily pain
CKD	Chronic kidney disease
CKD 2, 3, 4, 5	Specific stages of CKD
CKD 2-3 etc.	Range of specific disease stages (e.g. both CKD 3 and CKD 4)
CKD-ND	Chronic kidney disease, not on renal replacement therapy
CSM	Common Sense Model
CRP	C-reactive protein
CTT	Classical Test Theory
CVD	Cardiovascular disease
GFR	Glomerular filtration rate (ml/min/1.73m <sup>2</sup> )
ES	Effect size
ESA	Erythropoiesis-stimulating agents
ESRD	End stage renal disease. Kidney failure requiring renal replacement therapy, i.e. dialysis treatment or kidney transplant
GH	General health
Hb	Haemoglobin
HD	Haemodialysis
HRQoL	Health-related quality of life
IR	Illness representations, i.e. illness perceptions
IQR	Interquartile range
IPQ	Illness Perception Questionnaire
IPQ-R	Revised Illness Perception Questionnaire
JCS-60	Jalowiec Coping Scale
MAP	Mean arterial pressure
MCID	Minimal clinically important difference
MCS	Mental composite summary
MDRD	Modification of Diet in Renal Disease formula for estimated GFR
MH	Mental health
PAUS	Study cohort: ' <i>Prospective study of renal replacement therapy in Stockholm</i> '
PCS	Physical composite summary
PF	Physical functioning
PD	Peritoneal dialysis
PROGRESS	Study cohort: ' <i>Factors impacting progress of renal insufficiency</i> '
PTH	Parathyroid hormone
QoL	Quality of life
RE	Role emotional
RP	Role physical
RRT	Renal replacement therapy, i.e. dialysis treatment or kidney transplant
SF-36	Short Form-36 questionnaire
SNR/SRR	Svenskt Njurregister/Swedish Renal Registry

# 1 INTRODUCTION

A chronic condition like chronic kidney disease (CKD) usually has no cure. Therefore, patient experiences and patient related outcomes compose important care issues and are gaining increasing interest in evaluating and improving health care measures. Within chronic disease care, enhancing or maintaining health-related quality of life (HRQoL) is an important goal. In the progressive course of CKD, the individual's ability to manage the disease already in earlier stages has gained increased attention. Agreement on and adherence to treatment prescriptions are substantial in the efforts to slowdown disease progress. As CKD progresses, disorders and symptoms accumulate and the demands on the patient's self-management increase, which affects his/her health experience and everyday life. At the same time the individual's beliefs about his/her illness, treatment and own control and HRQoL are considered to influence each other and the individual's health behaviour (1, 2). A starting point for this thesis was a professional perspective of patient education, and an interest in self-management when living with CKD. However, few studies have examined illness perceptions and HRQoL in different stages of CKD up to initiation of dialysis treatment. Exploring this field may answer questions like 'How do people with CKD perceive their illness?', 'What symptoms do they experience?' and 'Which are the patterns of HRQoL in different stages of CKD?' The focus of this thesis was to explore how CKD affects thoughts, emotions, function and well-being. Increased knowledge of patients' illness perceptions and perceived HRQoL are important pieces in a comprehensive renal care that may contribute to improved self-management.

## 2 BACKGROUND

### 2.1 THE TRAJECTORY OF CHRONIC KIDNEY DISEASE

CKD is defined as a kidney damage manifested by structural or functional abnormalities of the kidney and/or a glomerular filtration rate (GFR)  $< 60 \text{ ml/min/1.73 m}^2$  for  $\geq 3$  months (3). The prevalence of CKD is approximately 10 % of the adult population (4). In a survey, the estimated prevalence of CKD in the Norwegian population was 2.7% in stage 1; 3.2% in stage 2; 4.2% in stage 3; and 0.2% in stage 4 (5). These proportions are comparable to those present in the Swedish population. In Table 1, the different stages of CKD and levels of kidney function are described, the higher CKD stage, the more severe the renal insufficiency.

*Table 1. Stages of chronic kidney disease (CKD) related to levels of kidney function, i.e., glomerular filtration rate (GFR) (National Kidney Foundation, 2002)*

CKD stage	Description	GFR (ml/min/1.73 m <sup>2</sup> )
1	Kidney damage with normal or increased kidney function	$\geq 90$
2	Kidney damage with mildly diminished kidney function	60 – 89
3	Moderately reduced kidney function	30 – 59
4	Severely decreased kidney function	15 – 29
5	Kidney failure	$< 15$

Glomerulonephritis is at present the most common kidney disease among prevalent patients on renal replacement therapy (RRT), and diabetes is the most common cause of kidney disease among incident patients in Sweden (6). Other common causes of CKD are hypertension, atherosclerosis and polycystic kidney disease.

The prevalence and incidence of RRT in Sweden are 903 and 125 per million inhabitants respectively, and the mean age for incident RRT patients in 2010 was 64 (men) and 62 (women) years (6). Two thirds of the Swedish RRT patients are men. Estimates by the Swedish Renal Registry (SNR/SRR) show a mean annual mortality for the whole RRT population in Sweden during 1991 – 2010 of 13.2 % (6). Seventeen percent of the Swedish population of patients with chronic kidney disease, not on renal replacement therapy (CKD-ND) had deceased before commencing RRT in 2011 (6).

Most kidney diseases tend to progress, and with declining kidney function multiple disorders gradually develop, such as anaemia, hypertension, inflammation, malnutrition, metabolic and mineral-bone disorders (7-9). CKD 1-3 are usually not associated with symptoms, although some disturbances may already have emerged. However, in CKD 4 symptoms accumulate, rather often insidious. Common symptoms appearing with renal insufficiency are fatigue, nausea, loss of appetite, thirst, loss of muscle mass, restless legs, cramps, itch and cognitive dysfunction (10, 11, 12 ). Furthermore, symptoms related to psychosocial aspects are commonly reported, such as sleep disturbances, anxiety and depression (13, 14).

#### 2.1.1 Comorbidity

CKD patients often suffer from comorbidities and complications such as cardiovascular disease (CVD) and chronic inflammation (9, 15), and CVD is the leading cause of morbidity and mortality in patients in CKD 3-5 (16-18). Congestive heart failure and CKD share some symptoms, such as fatigue, dyspnoea, edema, and impaired physical and cognitive function.

CKD can be seen as a complication of diabetes, but diabetes can also be a comorbid condition to CKD, and sometimes CVD is more likely to be considered as a complication of CKD than a comorbidity (19). CKD, CVD and diabetes are mainly caused by complex interrelationships between these conditions and shared risk factors (20), and conditions associated with increased CVD risk - like diabetes - are highly prevalent in CKD patients. Thus, the distinction between comorbidity and complication is not always clear.

A chronic low-grade inflammatory process is known to be present in mild as well as advanced CKD, presumed to be caused by disorders like decreased clearance of proinflammatory cytokines, increased oxidative stress, overhydration, and other biochemical disorders related to uremia (21, 22). Moreover, comorbid conditions, such as CVD and diabetes, are considered to increase the inflammatory process (23). Furthermore, relationships between inflammation and obesity as well as physical inactivity have been demonstrated (21, 24, 25). Inflammation can be assessed by different markers, of which C - reactive protein (CRP) is most commonly used. Previous research has indicated that elevated CRP levels were recognized in approximately 30% of CKD-ND patients and in about 50% of HD patients in Sweden (26). Inflammation in CKD has been linked to malnutrition, poor oral health, depression, atherosclerosis, vascular calcification and CVD (22, 26, 27). Elevated CRP levels is considered to be a strong predictor of CVD events and cardiovascular mortality (21, 23, 28). Apart from chronic inflammation, patients with kidney disease are exposed to a number of risk factors for developing CVD, such as hypertension, dyslipidemia, oxidative stress, anemia, mineral-bone disorders and arterial calcification (29). Other risk factors for CVD in CKD include older age, male gender, diabetes, smoking, albuminuria, overhydration, malnutrition and sleep disturbances (30). The risk (odds ratio) of CVD according to CKD stage in comparison with people without CKD increases from approximately 1.5 in CKD stage 2 to about 10 – 50 in stage 5, also depending on age and the degree of microalbuminuria (31).

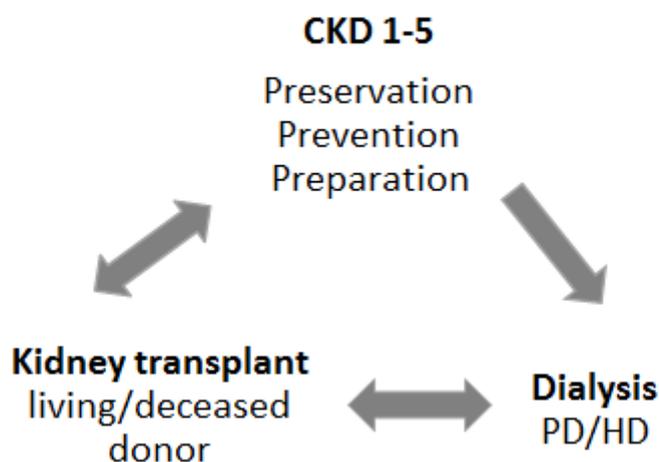
### **2.1.2 Management of CKD**

In Sweden, patients are generally referred to a nephrology outpatient clinic when GFR is about or below 40 ml/min/1.73m<sup>2</sup>. In early CKD stages, management is based on kidney diagnosis, blood pressure control and other risk factors, such as albuminuria, dyslipidemia, poor metabolic control in diabetic patients and life style issues like over/underweight, physical inactivity and smoking. In CKD 4-5, pharmacological treatment is usually intensified, with a pill burden that may comprise up to about 20 different drugs. Additionally this treatment is supplemented with dietary changes and occasionally fluid restrictions. Interventions to prepare for RRT (i.e. patient education and decision of RRT alternative), access surgery and/or preparing for kidney transplantation are commenced.

The treatment in all stages aims at preventing progression and complications of CKD (32). The individual's ability to manage his/her health situation and adherence to medication and diet prescriptions are crucial in the efforts to slow down the disease progress and prevent complications. Nursing focusing on CKD-ND patients includes measures based on education and counseling. These interventions focus on supporting and enhancing the patient's self-management, i.e. health literacy, symptom monitoring, management of medication and life style changes, and also aim to encourage the patient to reflect on his/her situation, perceived health, everyday circumstances and health-promoting factors (33-35).

RRT is usually commenced when the patient reaches end-stage renal disease (ESRD) at GFR approximately 5–10 ml/min/1.73m<sup>2</sup>. RRT options are peritoneal dialysis (PD), haemodialysis (HD) or kidney transplant, which all imply lifelong treatment (Figure 1). Some individuals – often elderly patients with multiple comorbid conditions – opt for

conservative management, aiming at preservation, preventing and managing complications and palliation. HD usually involves treatment sessions at least thrice weekly, carried out either at outpatient units or through self-care at home. PD means daily treatment procedures at home, usually as self-care, but may also be assisted. When a kidney transplant is rejected, the patient will return to dialysis treatment or a new transplant for survival.



*Figure 1. The care pathway for patients with CKD and renal failure*

### **2.1.3 Self-management**

Treatment of CKD-ND is focused on slowing down disease progression, reducing risk factors and preventing and/or managing disorders and complications. The treatment regimen is often complex, especially in advanced CKD stages, comprising careful medication with a rather high pill burden, diet and fluid restrictions and long-term adjustments of lifestyle. However, an efficient care requires self-management, and it is essential that the patient is in agreement with the treatment plan. Among patients with chronic diseases it has been shown that about 50% do not take their medications as prescribed (36, 37). Likewise, medication persistence – the length of time a patient continues to take a prescribed drug - tends to be low for those with chronic disease (38). Thus, it is evident that persons with CKD do have problems with integrating treatment regimens and imposing measures in their everyday lives (39). Self-management is a process that includes a broad set of attitudes, behaviour and skills. It has been defined as the knowledge to care for oneself and ability to make treatment related decisions, monitor symptoms, set goals and develop successful partnerships with health care providers (34, 40). Key components within self-management have been identified as medical management (self-care), role management (maintaining or creating new life tasks) and emotional management (coping with feelings evoked by the health situation) (34).

## **2.2 THEORETICAL FRAMEWORK**

### **2.2.1 Life-world and transitions**

The life-world theory derives from within the area of phenomenological philosophy and was developed by Husserl, Heidegger, Merlau-Ponty and Gadamer (41). Within nursing science, the life-world concept is indeed applicable and represents a cornerstone. It is essential to understand the patient's life-world in the process of promoting health (41). The life-world ('Lebenswelt') concept can be described as the subjective world in everyday life, with its objects and perceptions (42). It claims that we as human beings live in a directly perceived world interpreted and influenced by our feelings, beliefs, wishes and needs, and by our culture and language (43). The term illness refers to the subjective world, i.e. how

the individual experiences symptoms and perceives the disease (44). Illness is the subjective response to a disease or event, or what is “lived” by the patient and his/her family, including the meaning the patient gives to that experience (45). Chronic illness is defined by Lubkin & Larsen (p.5) as ‘...the irreversible presence, accumulation, or latency of disease states or impairments that involve the total human environment for supportive care and self-care, maintenance of function and prevention of further disability (44). Illness perceptions - i.e. illness representations (IR) - as well as perceived HRQoL compose important aspects of the individual’s everyday life when having a chronic disease. IR and HRQoL influence each other and the individual’s self-management and health behaviour (1).

Another central concept within nursing science is that of ‘transition’. The framework of transition, developed by Meleis et al (46) describes the nature of transitions, conditions, patterns of response and nursing interventions. Transition is about the way people respond to change and need to adapt to new circumstances in order to incorporate this change into their lives (47). It can be defined as a movement from one life phase or condition to another and may imply a changed perception of health, new meaning and sense of control (46, 48). Transitions both result in and are results of changes in life, health, relationships and environment. Health-illness changes may imply profound alterations in the lives of individuals and have important implications for their well-being and self-management ability (46, 49). Within renal care, reaching ESRD and commencing RRT is an example of a health-related transition.

## **2.2.2 Illness representations**

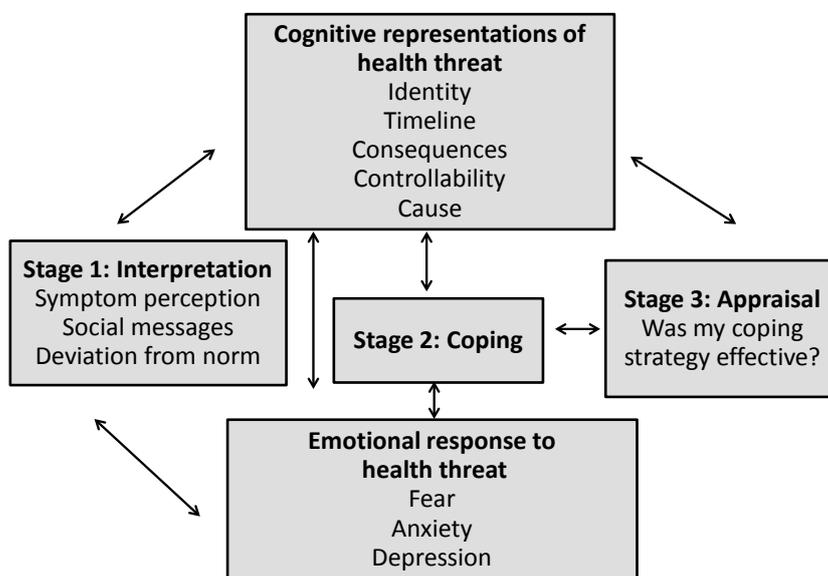
### *2.2.2.1 Definitions of IR*

Within the field of health psychology, people’s beliefs about health and illness and health behaviour have been examined (50). Health and illness beliefs could be described as a person’s individual cognitions and emotions about his/her health and/or illness, which influence health behaviour. A commonly used theory developed to explain health behaviour is the Health Belief Model (51). In this model, concepts like perceived susceptibility, severity, benefits, barriers and cues to action, and self-efficacy are stressed. Other commonly mentioned theories to explain health belief and health behaviour are that of attribution (52), health locus of control (53), and the transtheoretical model of motivational readiness and change (54). Health is also owing to how the individual manages stress, and coping refers to thoughts and actions people use to deal with stress. A widely used definition by Lazarus & Folkman is that coping means constantly changing cognitive and behavioural efforts to manage specific external or internal demands (55).

IR refer to how people understand and make sense of diseases or disabilities (56). When experiencing symptoms, people strive to find a label or explanation for this. Conversely, when a disease may be asymptomatic, people try - sometimes erroneously - to attribute symptoms to this “label” (57). An individual’s IR influences his/her health management and treatment outcomes (58, 59). It has been shown that more negative views of the illness are associated with poorer outcomes. Further, patients with the same disease can have different perceptions of their condition and the patient’s view of his/her disease may differ from that of health care providers. Moreover, the individual’s IR can be changed, offering opportunities to improve the patient’s adjustment to his illness. (57)

An influential theory of how people perceive and respond to their illness situation is the Common Sense Model of Self-Regulation (CSM), developed by Leventhal (50, 60, 61). It is considered as a dynamic system of goal setting, developing strategies and evaluating and revising goals and strategies (61, 62). Self-regulation is defined as conscious efforts to modulate thoughts, emotions and behaviour in order to achieve goals or normality in a

changing environment (63, 64). Consistent with cognitive models of behavioural process, the CSM treats the individual as an active problem solver, a common-sense “scientist” trying to make sense of his/her world (56). The CSM proposes that stimuli – such as symptoms - generate both cognitive and emotional representations of the illness. These representations are processed in three stages (Figure 2). First, the individual forms the representation of the illness. Cues to or information about illness come from symptoms, but also as social messages (i.e. from lay people as friends and family, diagnosis from doctor/caregiver, information from media). Cognitive factors and emotional reactions form an individual interpretation of the illness threat. In the second stage the individual adopts coping strategies to deal with the problem followed by a third stage, where the individual appraises/evaluates the efficacy of these behaviours. The model illustrates the individual’s self-regulating process by constantly assessing if coping is effective and whether the individual is successfully managing to achieve a renewed sense of equilibrium (50), and provides a useful conceptual framework for understanding health behaviour.



**Figure 2. Modified illustration of illness perception and the common sense model of self-regulation, based on Leventhal et al. (1980, 1984)**

Moreover, the CSM describes five dimensions that underlie the cognitive representations of illness. These dimensions provide a framework for patients to make sense of their symptoms, assess health risk, and direct action and coping. The five dimensions are defined as: Identity – labeling the illness and illness symptoms, Timeline – perceived course of the illness, Consequences - beliefs about the severity of the illness and its likely impact on physical, social and psychological functioning, Controllability – perceived management of the illness and Cause – personal ideas about the cause of the illness (61).

#### 2.2.2.2 Measurements of IR

The Revised Illness Perception Questionnaire (IPQ-R) (65) is a further development of the original Illness Perception Questionnaire (IPQ) (66). There is also a short-form version, called Brief IPQ (67). Other instruments for assessing IR are for example The Illness Cognition Questionnaire (68), the Implicit Models of Illness Questionnaire (69) and the Meaning of Illness Questionnaire (70). In recent years increased attention has been paid to exploring IR and their relations to HRQoL in different patient groups. In a range of medical conditions, research has illustrated a relationship between IR and HRQoL (71, 72). For

instance, if patients with coronary heart disease perceived their illness as accidental and experienced only a few symptoms, then they also experienced a better HRQoL (73). However, if patients with an acute condition as myocardial infarction perceived their illness as long-lasting, serious, less controllable and experienced more symptoms, then their HRQoL was also impaired (66). In progressive diseases like fibromyalgia and multiple sclerosis, it has been demonstrated that IR is an independent factor influencing HRQoL (74) and that illness perceived as serious related negatively to HRQoL (75). Research indicates that IR also predict several health related behaviours such as adherence to medication (76, 77), life style changes (78, 79) and coping (80). It has further been shown that IR, such as understanding and sense of control, are predictive factors for coping ability and health behaviour (72, 81). Moreover, patients' beliefs regarding symptoms, controllability, consequences and illness coherence explain coping behaviour (82, 83). By inference from earlier research it can be assumed that: (i) Illness related symptoms are expected to associate with coping strategies of avoidance and emotion expression. (ii) Perceived controllability can be expected to correlate to expressing emotions and problem-focused coping strategies. (iii) IR dimensions as identity, consequences, timeline and control can be expected to correlate to HRQoL (1).

Relatively few studies have evaluated the IPQ-R psychometrically, and cognitive interviews have rarely been accomplished in this procedure. The original IPQ and IPQ-R are generic and psychometric assessments need to be assured before using the questionnaire in specific disease groups (65, 84). In the literature review, a confirmatory factor analysis was performed in a cervical screening context (85). Further, a translation and validation among cancer patients in Greece showed good reliability and construct validity (86). However, the researchers stressed the probability for cultural differences. Results from psychometric analyses among patients with atopic dermatitis further indicated that the IPQ-R should be interpreted with care within this patient group (87). A Swedish translation of IPQ-R has recently been accomplished (88). However, that translation has not yet been psychometrically evaluated.

### 2.2.2.3 *IR and CKD*

IPQ and IPQ-R have been used and evaluated mainly in settings with patients on RRT, see Table 2. However, the causal attributions have not yet been explored. Associations were found between IR and HRQoL and well-being (71, 89, 90), depression (91), survival (92) and health behaviour with regard to medication and diet (93), and fluid restrictions (79). A study in 42 patients on HD treatment explored evidence for reliability and validity regarding the IPQ-R (89). The findings demonstrated acceptable internal consistency in all IPQ-R dimensions except for treatment control. Furthermore, the study showed that emotional representations and consequences correlated negatively to well-being. In a study including 109 CKD-ND patients, positive IR were found to associate with higher autonomy and self-esteem levels (2). Psychometric properties of the IPQ-R have, to our knowledge, not been assessed among CKD-ND patients.

**Table 2: Survey of studies (n=10) examining illness (IR) representations by IPQ-R in patients with renal insufficiency. Key word search in PubMed, National Center for Biotechnology Information (IPQ/illness representations kidney/renal ) → 17 articles → not written in English =1 excluded, not relevant to search topic =7 excluded**

<b>Author</b>	<b>Design/sample</b>	<b>Results</b>
Chilcot, 2010	N:99 HD patients	Lower consequence perceptions appeared to predict fluid non-adherence.
Chilcot, 2011	N:215 HD patients	IR were related to depression
Chilcot, 2012	Factor analysis, N:374 HD patients	IPQ-R found suitable for use in dialysis patients, but factor reliability not convincing.
Covic, 2004	N:82 HD patients. Age, (M, SD): 47.9 (12.1) Treatment duration (M, SD): 72 (50.6) months.	A higher personal control was associated with a lower emotional response and a better understanding of the illness. The perceived negative consequences of the illness were considerable, as was their emotional response. Four IR components were strongly related to HRQoL.
Daleboudt, 2011	Treatment intervention in lupus (SLE). N:16+16 patients with SLE and nephritis. Age, (M, SD): 35.3 (10.4) S-creatinine, umol/L (M, SD): 108.4 (57.4) 85.6 (44.7)	Treatment type in SLE may influence IR measured by Brief-IPQ.
Fowler, 2006	N:42 HD patients	Adequate reliability on all subscales except treatment control. IR related to well-being.
Griva, 2009	N:262 patients on RRT	IR more negative among dialysis patients than those with kidney transplant. Consequences and identity were inversely associated with HRQoL whereas control was positively associated with HRQoL.
Jansen, 2010	N:109 CKD-ND patients	Positive IR were associated with higher autonomy and self-esteem levels, but not with employment. IR were associated with autonomy and self-esteem. The perception of less treatment disruption was an important predictor.
O'Connor, 2008	N:73 HD patients	IR predicted self-care behaviour with regard to diet, fluid and medication.
Van Dijk, 2009	N:182 incident dialysis patients	IR related to survival.

## 2.2.3 Health-related quality of life

### 2.2.3.1 Definition of HRQoL

Quality of life (QoL) is a vague and difficult concept, with lack of consensus regarding definitions and interpretations (94). It is also complicated due to the essence as being subjective and uniquely personal (95). The term is used in a wide range of contexts, including the fields of psychology, sociology, economics, anthropology and demography. In general, the concept is about well-being or the final value of life for the person living it (96), ability to live a normal life, happiness/satisfaction, achievement of personal goals, social utility and physical and mental capability (95). According to the World Health Organization (WHO) QoL is defined as '*individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment*' (97). Ferrans & Powers have defined QoL as *a person's sense of well-being that stems from satisfaction or dissatisfaction with areas of life that are important to him/her* (98).

HRQoL is a subcategory of the wider QoL concept (94, 99), but the two concepts have fluid distinctions and are often used interchangeably. Although HRQoL is broader and not synonymous with the health concept, it is based on the WHO's definition of health (99), which states health as a state of '*complete physical, mental, and social well-being and not merely the absence of disease or infirmity*' (100). Health can also be understood in terms of different dimensions; as (i) a clinical status (biomedical approach), (ii) functional ability (holistic approach), (iii) well-being, (iv) a balance, or as a combination of two or more of these dimensions (101). The HRQoL construct is also lacking a single accepted conceptual definition. It has been argued that the term subjective health status should be used interchangeably with HRQoL (102), and that the concept HRQoL has been used inappropriately, when actually perceived health status is referred to (103, 104). Ferrans and co-workers (105) present a revised version of a conceptual model of HRQoL, developed by Wilson & Cleary (106). This revised model describes HRQoL as biological function, symptoms, functional status, general health perceptions, and characteristics of the individual and of the environment. Another model, depicted by Stuijbergen and co-workers, putting more emphasis on health promotion and chronic conditions, outlines concepts such as illness severity, barriers, resources, self-efficacy, acceptance and health promoting behaviour (107). This model supports the assumption that HRQoL is the outcome of a complex interplay among severity of illness, antecedent variables and health-promoting behaviour.

Although there are several definitions, it is agreed that HRQoL is temporal, subjective and multidimensional in nature, reflecting at minimum physiological, psychological and sociological aspects (95, 99). A definition that suits this thesis is that of HRQoL as the subjective assessment of the impact of disease and its treatment across the physical, psychological and social domains of functioning and well-being (108).

### 2.2.3.2 Measurements of HRQoL

Today, several instruments to assess HRQoL are available. Instruments for measuring HRQoL can be divided into two broad categories: generic and disease-specific measures (94, 109). Generic instruments are constructed to be used in any condition and also in the general population. They have been criticized for not capturing disease-specific issues or problems, but on the other hand they allow comparisons between different groups and conditions and with general populations. Condition-specific instruments are more focused on a specific condition and disease-specific symptoms.

### 2.2.3.3 *HRQoL in CKD patients*

Impaired HRQoL – especially in physical functioning - is well described among patients on dialysis treatment and found to correlate to factors such as symptom burden, hypertension, anaemia, nutritional status, dialysis modality, depression, cognitive dysfunction and frailty (10, 110-113), see Table 3. Moreover, associations between HRQoL and education, depression, exercising habits (114), proteinuria (115) and inflammatory status (116) have been found, see Table 3. Although limited data is published on the associations between comorbidity and HRQoL in patients with CKD (19), it has been shown that the presence of comorbidities often implies impaired HRQoL and poorer prognosis (20, 117). CVD (118) as well as diabetes (119) have both been described as conditions associated with affected HRQoL. It has also been shown that diabetic patients have worse HRQoL than non-diabetic patients when commencing dialysis (120).

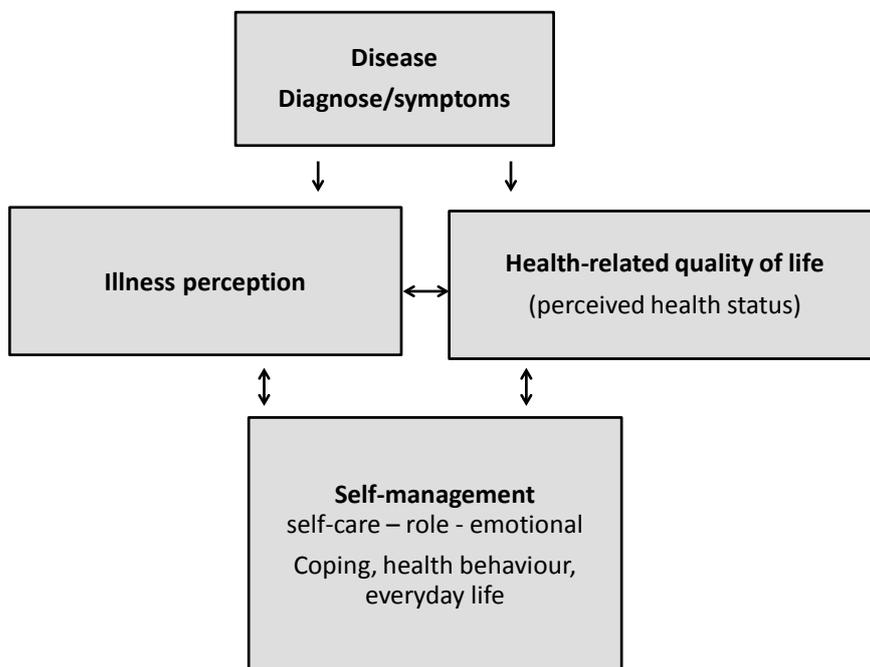
Further, low HRQoL scores in dialysis patients have proved to be strong and independent predictors of hospitalization and mortality (121-123). Some studies have however, demonstrated deteriorated HRQoL already in CKD 2-5, in particular in physical health (114, 124, 125) but also in mental health (126). When following patients in CKD 3-5 up to four years, it was shown that HRQoL deteriorated over time, especially in those with a history of congestive heart failure (124). Impaired HRQoL have also been shown shortly before (0-4 weeks) initiation of dialysis treatment (127).

**Table 3: Survey of studies (n=10) examining HRQoL in CKD-ND patients.** Key word search in PubMed, National Center for Biotechnology Information (HRQoL + CKD) → 33 articles → not adult patients=6 excluded, patients on RRT=5 excluded, reviews or discussion=10 excluded, not written in English =1 excluded, no data reported=1 excluded

Author	Instrument and design/sample	Results
Abu-Alfa, 2008	KDQOL. Interventional, N:277 GFR (M, SD): 25.1 (9.1) Age, (M, SD): 67.1 (13.1)	Significantly improved RQoL with ESA treatment.
Alexander, 2007	KDQOL. Interventional, N:48 GFR (M, SD): 21.5 (1.4) Age, 18–64 (M, SD): 21 (43.8), age ≥ 65: 27 (56.3)	Improved haemoglobin was associated with statistically significant clinically meaningful HRQOL improvements on scales measuring physical activity, vitality and fatigue.
Chin, 2008	SF-36. Prospective cohort, N:944 GFR (M, SD): 61.1 (12.8) Age, (M, SD): 76 (8.6)	Significantly decreased HRQoL among participants with a GFR value of <45 ml/min/m <sup>2</sup> compared to the other GFR groups. GFR <45 was an independent predictor of poor physical HRQOL. Age, gender, education, exercising habits, depression and history of cardiovascular accident, were also predictors of HRQOL
Farag, 2011	KDQOL. Prospective observational, N:69 GFR (M, SD): 43.7 (28.8) Age, (M, SD): 56.3 (17.8)	Anemic patients had significantly worse HRQoL than non-anemic. Reduced HRQOL in anemic patients related to both anemic and inflammatory status.
Kelley, 2007	KDQOL. Longitudinal, N:44 Type 2 diabetes nephropathy GFR (M, SD): 44 (31) Age, (M, SD): 66 (9)	Proteinuria was a predictor of impaired HRQOL.
Molsted, 2007	KDQOL. Cross-sectional, N:63 GFR (M, SD): 21.4 (9.9) Age, (M, SD): 65 (12)	CKD patients scored lower than the general population. Most pronounced impairment was found in physical capacity. Tobacco consumption was independently associated with low HRQOL scores.
Mujais, 2009	KDQOL. Prospective observational, N:1186 GFR (M, SD): 25.6 (0.3) Age, (M, SD): 65.6 (0.4)	Baseline HRQOL was reduced in proportion to the severity grade of CKD. Physical functioning and role-physical scores declined progressively with more advanced CKD stages. Female gender, presence of diabetes and history of cardiovascular comorbidities were associated with reduced HRQOL, as were anemia and beta blocker usage. The main correlates of change over time were age, albumin level and co-existent comorbidities.
Perlman, 2005	SF-36. Prospective observational, N:634 GFR (M, SD): 23.6 (9.6) Age, (M): 60.7	HRQoL scores were higher in CKD cohort than in HD patients, but lower than in controls. GFR was not significantly associated with HRQoL. Haemoglobin level predicted HRQoL.
Porter, 2012	SF-36. Cross-sectional, N:639 GFR (M, SD): 43.8 (17) Age, (M): 60	Association found between CKD and low HRQOL. Significant positive association between higher kidney function level and PCS, but not in MCS.
Tajima, 2010	Euro-QOL (EQ-5D). Cross-sectional, N:537 GFR (M, SD): 56.1 (34.1) Age, (M, SD): 55.2 (1)	HRQOL decreased with progression of CKD and/or presence of anemia, under-nutrition, hypertension, diabetes, or history of CVD.

### 2.3 RATIONALE FOR THE THESIS

Symptoms, function in everyday life and well-being are important patient outcomes when evaluating and improving health care in chronic diseases (128), and HRQoL is a significant key indicator in how a condition affects the patient's life. It is of importance to study and understand IR and HRQoL in CKD patients, since they interrelate and also have impact on the patients' self-management and health behaviour. Self-management is owing to illness and health perceptions (Figure 3), which may comprise important outcome measures of renal care quality. Exploring IR and HRQoL measures can therefore provide a deeper understanding of how CKD patients perceive their health, illness and symptoms, and how they conceptualize and adjust to their CKD. Attending to the individual's IR and HRQoL may be helpful in guiding and supporting self-management within renal care. Since the IPQ-R is generic and psychometric assessments for a Swedish, disease-specific version were lacking, this needed to be assured before use in clinical practice.



*Figure 3. Outline of relations between illness representations, health-related quality of life and self-management.*

### **3 AIMS**

It was hypothesized that:

- Construct validity of the IPQ-R in a CKD-ND context would be supported
- IR would correlate to HRQoL and coping
- Declining kidney function, and more symptoms correlate with more negative IR on an individual basis
- HRQoL would decline with impaired kidney function
- HRQoL would be negatively affected by comorbidity, age and gender

#### **3.1 OVERALL AIMS**

To explore IR and HRQoL in patients in CKD stage 2-5

#### **3.2 SPECIFIC AIMS**

- I To evaluate psychometric properties of a Swedish translation of the IPQ-R, adapted to adults in CKD-ND, stage 2-5 (study I)
- II To investigate HRQoL in patients in different stages of CKD up to initiation of dialysis treatment and to explore possible correlating and influencing factors (study II)

##### **3.2.1 Research questions**

- Is construct validity of the IPQ-R questionnaire supported in a Swedish CKD-ND context?
- How do people with chronic kidney disease (CKD-ND) perceive their illness, with respect to causes, symptoms, consequences, predictability, emotional reactions, control and illness coherence?
- Is there an interrelationship between IR and HRQoL in a CKD-ND context?
- Which are the patterns of HRQoL in different stages of CKD?

## 4 MATERIAL AND METHODS

### 4.1 DESIGN

The studies were conducted to explore and evaluate IR and HRQoL in patients with different stages of CKD. Designs are presented in Table 4.

*Table 4. Description of design, variables and methods used in the studies*

	Study I	Study II
<b>Aims</b>	To evaluate IPQ-R in a group of adult Swedish patients with CKD-ND	To explore HRQoL in a group of adult Swedish patients with CKD, stage 2-5 up to initiation of dialysis treatment, and to explore correlating and predicting factors
<b>Design</b>	Exploratory, evaluational <i>Part 1:</i> Qualitative approach Usability evaluation: Content validity, cognitive interviews <i>Part 2:</i> Quantitative approach Psychometric testing (internal consistency, test-retest reliability, concurrent and convergent validity)	Quantitative approach Exploratory Cross-sectional
<b>Demography</b>	<i>Part 1:</i> Age, sex, marital status, educational level <i>Part 2:</i> Age, sex	Age, sex
<b>Clinical variables</b>	Illness representations Health-related quality of life Coping strategies Disease stage, renal diagnose	Health-related quality of life Disease stage, GFR-level, renal diagnose, comorbidity, BMI, blood pressure, CRP, haemoglobin, p-albumin
<b>Instruments</b>	IPQ-R questionnaire SF-36 questionnaire JCS-60 questionnaire	SF-36 questionnaire
<b>Subjects</b>	7 patients (interviews) 54 patients(psychometrics)	535 patients + 55 controls
<b>Statistics and Tests</b>	Descriptive, comparing groups, Spearman's correlation coefficient, Crohnbach's $\alpha$ , Wilcoxon Signed Rank Test Chi-sqaure Kruskal-Wallis Mann-Whitney U	Descriptive, comparing groups, ANOVA oneway Test Cohen's $d$ multiple linear regression (enter method) Independent T-test Chi-sqaure Mann-Whitney U

### 4.2 PSYCHOMETRIC CONCEPTS

Psychometrics can be described as the science of measuring psychological properties (129). It includes fields such as knowledge, abilities, attitudes, personality traits and education. Psychometrics is primarily concerned with the construction and validation of measurement instruments such as questionnaires and tests. Psychometric properties relate to the data collected on a test to determine how well it measures the specific construct. Psychometric properties within the Classical Test Theory (CTT) are usually defined as reliability and validity. CTT and psychometrics are underpinning scale construction. The concept of reliability derives from CTT, which states that any observation is composed by two components; a true score (T) and an error score ( $\text{Score}_{\text{Observed}} = \text{Score}_{\text{True}} + \text{error}$ ) (130).

**Reliability** refers to consistency and repeatability of a measure. It is a measure of the proportion of the variability in scores which is due to true differences between individuals, expressed as a number between 0 and 1, where 0 indicates no reliability and 1 indicates perfect reliability. Reliability can be measured by **internal consistency** (inter-item reliability), assessing the consistency across items within a questionnaire, i.e. measuring the average of correlations among all items in a questionnaire, assuring that all items are measuring the same construct. As the inter-correlations among test items increase the Cronbach's alpha coefficient will generally increase. Another measure of reliability is **stability**, assessing the repeatability of the questionnaire. Thus the questionnaire is distributed to the same patients on two occasions separated by some time interval, assuming that there should be no substantial change. The test-retest is estimated by correlation. In evaluating the IPQ-R questionnaire, the Cronbach's alpha was used to calculate inter-correlations, and the test-retest reliability was used to measure stability (Table 5).

**Validity** is the extent to which a test measures what it claims to measure. Validation can be divided into different aspects, like construct validity, content validity, and criterion-related validity. **Construct validity** is assuring that the test actually (in reality) measures what the theory says it does and can be seen as an overarching category of validity. **Face and content validity** are two validity forms to judge whether the questionnaire-instrument is appropriate for the intended purpose. Both face validity and content validity are non-statistical and concern a subjective judgment of whether a test looks reasonable and seems to assess desired qualities, whether it covers relevant or important content or domains. They are both performed by one or more experts. Cognitive interviewing is often used when evaluating usability and content validity. A test is assumed to have **criterion-related validity** when it correlates with other criterion measures. This type of validity can further be divided into subcategories, such as concurrent, predictive, convergent and discriminant validity. **Concurrent validity** refers to the ability to distinguish between groups the test theoretically should be able to, and **predictive validity** refers to the ability to predict what the test is theoretically able to predict (131). **Convergent validity** assesses correlations with other variables or measures of the same construct (to which it should be related), and **discriminant validity** refers to demonstrating that the test does not correlate with dissimilar variables. Strategies chosen to provide evidence of validity in this thesis were face and content validity, concurrent validity and convergent validity (Table 5).

Other methods and concepts within psychometrics are **factor analysis, sensitivity to change and responsiveness**. Factor analysis is a procedure to evaluate how underlying constructs influence the responses of a set of variables. Sensitivity to change can be defined as an instrument's ability to measure any degree of change, and responsiveness as its ability to measure clinically important changes (132). They can both be regarded as a form of construct validity (130).

**Table 5. Assessment of construct validity of the IPQ-R for patients with CKD-ND**

Type of reliability/validity	Procedure
Internal consistency (inter-item reliability)	Cronbach's alpha coefficient
Stability	Test-retest
Content	Review by expert panel (face validity: renal nurses) Cognitive interviews: CKD patients
Concurrent	Distinguish ratings between different patient groups
Convergent	Inter-correlations between IPQ-R dimensions Correlation with other construct related measure (SF-36, JCS-60)

## 4.3 PARTICIPANTS AND SETTINGS

### 4.3.1 Study I

In study I, patients in CKD stage 2-5 controlled at Karolinska University Hospital participated. The study was performed in two sections: In part one, 7 patients (five men and two women) in CKD stage 2-5 were purposively recruited in 2007-2008 for cognitive interviews for evaluation of usability and content validity. The participants had CKD of various origins, their median age was 37 years (Range: 34-84) and median disease duration was 20 years (Range: 7-30). Five had an educational level at university degree and all participants were living with a spouse or partner. The method of cognitive interviewing is widely used when pre-testing questionnaires in order to explore cognitive processes that respondents are using (133). The aim is to retrieve information regarding how questions/statements are comprehended and answered, effects of the order of the questions/statements and attitudes to the content in order to identify and correct problems within the questionnaire. Cognitive interviewing with the retrospective verbal probing technique means that people verbally report their mental activity immediately after having taken part of a questionnaire (133). The interviews in this study were carried out as follows: A cognitive testing protocol was developed, consisting of the translated and modified IPQ-R along with standard probe questions. All interviews (60 – 90 minutes respectively) took place at Karolinska University Hospital in Sweden, and were audio-taped. Each participant was asked to read, fill in and note any reflection regarding the statements in the IPQ-R. Immediately after having completed the questionnaire, the participants were interviewed through retrospective probing considering how they understood the statements and how they came to an answer.

In part two, 80 patients were asked and 54 accepted to participate in the testing of psychometric properties. The participants were recruited in 2008 - 2010. Forty of the participants were recruited from a prospective observational cohort study and 14 through consecutive recruitment at Karolinska University Hospital. A selection of variables describing the participants is presented in Table 6. After acceptance, the questionnaires were mailed together with written information in a missive letter to the participants.

**Table 6. Patient characteristics, study I-II**

Parameter	Study I	Study II
Patients, N	54	535
Age, years, Md (IQR) or M (SD)	56 (43-62)	61 (15)
Females, N (%)	23 (42,6)	175 (33)
CKD 2-3, N (%)	35 (65)	54 (10)
CKD 4-5, N (%)	19 (35)	481 (90)
Haemoglobin (mg/L), Md (IQR) or M (SD)	130 (120-139)	115 (17)
P-Albumin (mg/L), Md (IQR) or M (SD)	36 (33-39)	34 (5.5)
Primary glomerulonephritis, N (%)	17 (31.5)	95 (18)
Secondary glomerular systemic disease*, N (%)	3 (5.5)	46 (9)
Diabetes, N (%)	8 (15)	158 (30)
Familial, hereditary renal disease, N (%)	11 (20.3)	58 (11)
Vascular disease, N (%)	4 (7.4)	115 (22)
Other, N (%)	11 (20.3)	101 (19)

\*Secondary glomerular systemic diseases except for diabetic nephropathy

### 4.3.2 Study II

In this cross-sectional study 535 patients in CKD 2-5, with a GFR ranging from 69 to 2 ml/min/1.73m<sup>2</sup>, and 55 controls from the Stockholm region in Sweden were assessed for HRQoL through the SF-36 questionnaire (Table 7). Register data from two prospective

observational studies (PROGRESS and PAUS) and the local (outpatient clinic, Karolinska University Hospital, Solna) Swedish Renal Registry (SNR/SRR) were collected and merged (Table 7). The participants in the PROGRESS (*Factors impacting progress of renal insufficiency*) cohort (n=104) were recruited by convenience at the renal outpatient clinic at Karolinska University Hospital during 2002-2009. These participants had a kidney function corresponding to CKD 2-3 or 4-5. In the PAUS (*Prospective study of renal replacement therapy in Stockholm*) cohort, 532 patients were recruited consecutively from eight nephrology units in Stockholm when initiating dialysis treatment during 2000-2005. Of these, 330 patients from seven units participated in the HRQoL survey. In this cohort, 97% of the participants had a kidney function, corresponding to CKD 5. From the local SNR/SRR cohort (n=468), 116 patients were recruited by convenience for HRQoL assessments in connection to visits at the renal outpatient clinic at Karolinska University Hospital during 2004-2009. These participants had a kidney function corresponding to CKD 3-5. In the multiple linear regression analyses, a random sample of 70 patients was drawn from the CKD 5 group and collapsed with CKD 2-4 data, creating a CKD 2-5 group of 211 patients. Controls, matched for age, sex and living area to the CKD 2-3 patients were recruited. Of these, 31 were randomly selected from the Swedish Register of the Total Population and 24 recruited through the web site of the Karolinska University Hospital. Inclusion criteria for the controls were GFR  $\geq 80$  ml/min/1.73m<sup>2</sup>, absence of kidney disease, CVD, diabetes and any ongoing medication. A selection of variables describing the patients is presented in Table 6.

**Table 7. Participant flow chart, study II**

Study cohort, n	CKD stage	Patients in HRQoL survey, n	Drop-out* n	n	Participants, n GFR# ranges and CKD stages
PROGRESS: 104	→2 - 5	→104	2	→102	} 535 CKD stage 2 GFR range 60-69 31 CKD stage 3 GFR range 31-58 23 CKD stage 4 GFR range 15-29 87 CKD stage 5 GFR range 2-14 394 Controls### 55 All participants 590
SNR/SRR: 468	→3 - 5	→116		→116	
PAUS: 532	→4 - 5	→330	13	→317	

# GFR= Glomerular Filtration Rate, ml/min/1.73m<sup>2</sup>

##GFR  $\geq 80$ , matched to patients in CKD stages 2-3.

\*drop-out due to incomplete responses

## 4.4 DATA COLLECTION

### 4.4.1 Study I

#### 4.4.1.1 Content validity and usability evaluation

Step one: *Face- and content validity* was evaluated through the following procedures: (i) The IPQ-R was translated from English to Swedish by the investigators. (ii) A bilingual person within medical care performed a back translation. (iii) The translations were compared, differences discussed and adjustments agreed by the research group. (iv) The IPQ-R items in the illness identity part were adjusted to CKD patients. Recognized disease-specific symptoms were added (12). Moreover, two core identity items – sore throat and sore eyes – were deleted, since they were considered irrelevant in this context. (v) An expert panel of experienced renal nurses reviewed the translated and modified IPQ-R. Further adjustments to translation and symptoms were implemented and a pilot version of a Swedish translation modified to CKD was accomplished. Except for the identity dimension, all original items remained intact in this version. Statistics Sweden was consulted and provided feedback concerning the format design.

In step two, *usability- and content validity* were assessed through cognitive interviews using the retrospective verbal probing technique (133). The pilot version was assessed and validated by CKD patients. This was accomplished through cognitive interviews with the retrospective verbal probing technique. After seven interviews informational saturation was reached. Each interview was transcribed verbatim into a protocol, reporting general impressions, summary of comments on the different parts of the questionnaire and a statement-by-statement review, i.e. for each statement all comments on that item were compiled. The transcripts were reviewed for identification of words, word strings in order to recognize any problems with the questionnaire. Subsequently to the interviews, further adjustments were made on the IPQ-R, such as clarifying the instructions, adding more disease-specific symptoms and changing some terms to more appropriate synonyms. A final version of the translated IPQ-R was created. This version contained 56 statements (translated from the original) added with 29 items (whereof 12 original core items and 17 disease-specific symptoms) on illness identity. In concordance with the results from the interviews, the items concerning whether experienced symptoms are considered to relate to CKD were complemented with the response alternative “*do not know*”.

#### 4.4.1.2 *Psychometric test evaluation*

In the psychometric test evaluation, 54 patients (response rate 68%) in CKD-stage 2-5 completed the following questionnaires: The translated and modified version of IPQ-R, Short Form-36 (SF-36) and Jalowiec Coping Scale (JCS-60). To test the reliability, 40 of the 54 responding patients were also asked to complete the IPQ-R re-test two weeks after having returned the first questionnaire. Thirty-four patients (response rate 85%) completed the retest. The questionnaires were mailed together with written information in a missive letter to the participants. All questionnaires were completed home and returned by mail.

### 4.4.2 **Study II**

Register data from the three study cohorts were collected and merged (see Table 7).

#### 4.4.2.1 *HRQoL measures*

The patients from all three cohorts and the controls were asked to complete the SF-36 by self-administration in connection with their visits at the nephrology units. In the PAUS cohort SF-36 was collected at or up to two weeks after first dialysis session.

#### 4.4.2.2 *Biomarkers*

Biomarkers for all participants (including the controls) were blood test analyses, blood pressure, weight and length. Blood test analyses were haemoglobin (Hb), albumin, C-reactive protein (CRP), phosphate, parathyroid hormone (PTH) and creatinine. Moreover, GFR was determined in all participants. In the controls and the patients in CKD 2-3 GFR was examined by Iohexol-clearance, and in all other patients GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula (134, 135). Blood pressure was measured in horizontal or sitting position and mean arterial pressure (MAP) was calculated as the sum of diastolic blood pressure and one third of the difference between the systolic and the diastolic blood pressure. Weight measures were performed and Body Mass Index (BMI) was calculated by dividing the individual's weight by the square of his/her height.

### 4.4.3 **Questionnaires**

#### 4.4.3.1 *The Revised Illness perception Questionnaire (IPQ-R)*

The IPQ (66) and later the IPQ-R (65) questionnaires were developed as measures to identify IR and is asking individuals for their own beliefs about their condition. The five dimensions that underlie IR are defined as: Identity – labeling the illness and illness

symptoms, Timeline – perceived course of the illness, Consequences - beliefs about the severity of the illness and its likely impact on physical, social and psychological functioning, Controllability – perceived management of the illness and Cause – personal ideas about the cause of the illness (61). In the IPQ-R version (study I), the dimensions Timeline cyclical, Illness coherence and Emotional representations are added, and the controllability dimension is divided in two subscales. The questionnaire is generic, and may need disease-specific adjustments regarding symptoms. Item examples in each IR dimension are illustrated in Table 8. The items are rated by the respondent on a five-point Likert scale ranging from “strongly disagree” to “strongly agree” (scored 1-5). The original IPQ-R contains 56 statements and 14 proposed items on symptoms/illness identity. In a factor analysis of the causal items based on data from eight illnesses, the originators of the IPQ-R concluded four primary factors of causal attributions (65). These cause categories were labeled psychological attributions, risk factors, immunity, and chance.

**Table 8. IPQ-R dimensions, items and scoring range. ([www.uib.no/ipq](http://www.uib.no/ipq))**

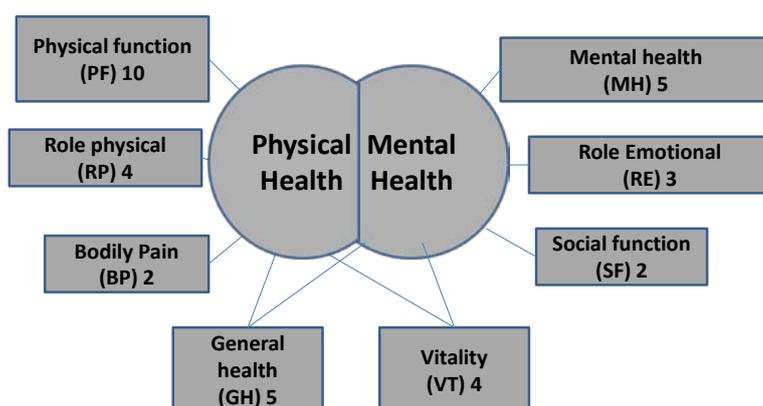
Dimensions	Item examples	N items	Scoring range*
Identity	<i>Symptoms that the patient sees as part of the illness</i>	14	
Timeline	<i>My illness is likely to be permanent rather than temporary</i>	6	6 - 30
Timeline cyclical	<i>My illness is very unpredictable</i>	4	4 - 20
Consequences	<i>My illness is a serious condition</i>	6	6 - 30
Personal control	<i>I have the power to influence my illness</i>	6	6 - 30
Treatment control	<i>My treatment can control my illness</i>	5	5 - 25
Illness coherence	<i>My illness doesn't make any sense to me</i>	5	5 - 25
Emotional	<i>I get depressed when I think about my illness</i>	6	6 - 30
Cause	<i>Stress was a major factor in causing my illness</i>	18	

\*High scores on the identity, timeline, consequences, cyclical and emotional dimensions represent strongly held beliefs about the number of symptoms attributed to the illness, the chronicity of the condition, the negative consequences of the illness, the cyclical nature of the condition and negative feelings connected to the illness (like anxiety, worry, anger, fear, depression). High scores on the personal control, treatment control and coherence dimensions represent positive beliefs about the controllability of the illness and a personal understanding of the condition.

#### 4.4.3.2 The 36-item short-form Questionnaire (SF-36)

SF-36 (study I, II), is a self-administered generic HRQoL questionnaire, not specific to any disease or treatment group. The SF-36 is covered by a conceptual model of HRQoL (136) and includes 36 items that yield an 8-dimension profile on a 100-point scale, a higher score indicates a better perceived health state. The eight dimensions are: Physical functioning (PF, 10 items), Role limitations caused by physical problems (RP, 4 items), Bodily pain (BP, 2 items), General health (GH, 5 items), Vitality/energy/fatigue (VT, 4 items), Social functioning (SF, 2 items), Mental health/emotional well-being (MH, 5 items) and Role limitations caused by mental health/emotional problems (RE, 3 items) (Figure 4). The items refer to perceived health status during the last 4 weeks. The lowest possible score in the PF scale is defined as great limitation in performing all physical activities, including self-care activities such as bathing and dressing, in BP as very severe and limiting pain, in VT as feeling tired and worn out and in MH as feelings of nervousness and depression all the time. The lowest possible score in SF is defined as frequently disturbed normal social activities due to health problems, and in RP and RE as limitations in work or other daily activities due to physical and mental or emotional problems respectively. The PF, RP, BP and GH dimensions are usually summarized into a physical composite summary (PCS) and the VT, SF, MH and RE dimensions summarize to a mental composite summary (MCS) (137, 138). The mean scores of the Swedish reference population (n=8930) aged 15-93 are: PF=87.9, RP=83.2, BP=74.8, GH=75.8, VT=68.8, SF=88.6, RE=85.7, MH=80.9, the mean summary scores

(n=8004) are: PCS=50 and MCS=50 (139). The SF-36 (version 1.0) was used as it covers relevant domains of function and well-being, and most of the items in SF-36 are considered to have good sensitivity and responsiveness (109). SF-36 has been used world-wide and been recognized in CKD patients as well as in various contexts. Thus it permits comparison within and between other conditions as well as comparison to controls or general population. It has been proved valid and reliable (94, 139) and recommended by the National Kidney Foundation guidelines (140).



**Figure 4.** SF-36 scale dimensions and item numbers. Modified from [www.sf-36.org](http://www.sf-36.org)

#### 4.4.3.3 Jalowiec Coping Scale Questionnaire (JCS-60)

JCS-60, part A (study I) measures the use of cognitive and behavioural coping strategies. Coping refers to thoughts and actions we use to deal with stress. A widely used definition by Lazarus & Folkman (55) is that coping means constantly changing cognitive and behavioural efforts to manage specific external or internal demands. The JCS-60, developed by Jalowiec (141), has been translated, validated and tested for use in Sweden (142). It contains 60 items within following eight subscales: Confrontive (confronting the situation, facing up to the problem, constructive problem-solving), evasive (evasive and avoidant activities), optimistic (positive thinking, positive outlook, positive comparisons), fatalistic (pessimism, hopelessness, feeling of little control over the situation), emotive (expressing and releasing emotions, ventilating feelings), palliative (trying to reduce or control distress by actions to feel better), supportant (using support systems: personal, professional, spiritual) and self-reliant (depending on yourself rather than on others in dealing with the situation) coping style (141).

## 4.5 ETHICAL CONSIDERATIONS

The studies were approved by the Regional Ethical Review Board in Stockholm, Sweden. Informed consent was obtained from all participants in study I and in those included in the PROGRESS and PAUS cohorts. Patients from the local SNR/SRR cohort received information with presumed consent when being included in the registry, and they also gave their informed consent when they were asked to respond to the SF-36 questionnaire. In study I, the patients recruited for interviews were informed about the aim, the technique for

cognitive interviewing, including the tape recording, and had given their consent beforehand. All respondents were given home visits as an option for the interviews. This alternative can be seen as measure to facilitate the patients' comfort and get away from the hospital environment. On the other hand, it may be seen as an intrusion into one's private sphere. All respondents chose to attend to the hospital, where the interviews were accomplished in a secluded room.

Almost all of the respondents in the interviews (study I) spontaneously expressed their appreciation for having the opportunity to participate and reflect over their situation and being "listened to". In the psychometric testing (study I), the questionnaires were mailed together with thorough information regarding the study, contact details and consent form in a missive letter to the participants. The completed questionnaires were returned by mail together with a signed written consent to the investigators.

To use questionnaires in health care requires ethical considerations, since asking questions about health, perceptions and personal feelings are to be regarded as delicate matters, and require tactfulness and respectful management from the caregiver or researcher.

It is important that the principles and quality standards of Good Clinical Practice (provided by The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) and the Declaration of Helsinki are complied with, assuring aspects such as the participants' integrity and voluntarism (143). However, an ethical dilemma concerning voluntarism may arise when you as caregiver and researcher recruit on your own clinic. A dependency situation may occur, where the patient might feel uncomfortable to decline participation. It is important that the researcher is aware of this. In the present studies, voluntarism concerning the participation was emphasized.

## **4.6 STATISTICAL METHODS**

All statistical methods used in the studies are listed in Table 4. IBM® SPSS® Statistics software (SPSS Inc., Chicago, IL, USA 2006), version 15 and 20 were used for the statistical analyses.

### **4.6.1 Study I**

As data was not normally distributed, non-parametric statistics were used (144). *Internal consistency* of the IPQ-R was analyzed using Cronbach's alpha ( $\alpha$ ) and assessed according to guidelines, i.e.  $\alpha >.7$  = acceptable (145). *Test-retest reliability* was analyzed by using Spearman's correlation coefficient for ranked data and Wilcoxon Signed Rank Test. P-value  $<.01$  was selected as level of statistical significant difference. *Inter-correlations* between IPQ-R dimensions were analyzed by Spearman's correlation coefficient for ranked data. Effect magnitudes were estimated according to guidelines, i.e. correlation coefficient  $>.5$  = large magnitude;  $.5 - .3$  = moderate magnitude;  $.3-.1$  = small magnitude;  $<.1$  = insubstantial magnitude (146). *Concurrent validity* was analyzed by using the Kruskal-Wallis Test and post hoc Mann-Whitney U-Test to compare ratings between patient groups. P-value  $<.05$  was selected as level of statistical significance. *Convergent validity* was analyzed by using Spearman's correlation coefficient for ranked data to identify correlations between IPQ-R, SF-36 and JCS-60 questionnaires. Effect magnitudes were estimated according to guidelines, i.e. correlation coefficient  $>.5$  = large magnitude;  $.5 - .3$  = moderate magnitude;  $.3-.1$  = small magnitude;  $<.1$  = insubstantial magnitude (146).

### **4.6.2 Study II**

Raw scores from the questionnaires were transformed to scale scores using the software syntax for SF-36 (139). Data was analyzed and presented according to outcome of

distributions of normality tests. Chi-square test was used to analyze differences in nominal-level variables. Independent t-test was used to compare mean HRQoL scores related to categorized correlates (gender, history of comorbidity, age, GFR, Hb, p-albumin, CRP, blood pressure, BMI). Cut-off value for age was set at the mean for the whole patient group, i.e. 61 years. Other correlate cut-off values were set in accordance to clinical guidelines, research findings and expertise knowledge, such as GFR at 45 ml/min/1.73m<sup>2</sup>, Hb-value at 110 g/L, CRP at 5mg/L, p-albumin at 35 g/L, MAP at 110 mmHg and BMI at 20 and 30. Data from CKD 2 and 3 were pooled, as there were no significant differences in SF-36 scores between these groups. Differences in HRQoL between CKD 2-3 and the matched controls were evaluated by the Mann-Whitney U-test. HRQoL differences between the three patient groups were analyzed by the ANOVA one-way test. The magnitude of differences in HRQoL scores was assessed using Cohen's *d* formula (146). Cohen's *d* is a standardized measure of effect size (ES) and is computed as the difference between the mean scores of the compared groups divided by the pooled within-group standard deviation (SD). The Cohen's *d* was computed, using the calculator elaborated by Becker (147). According to Cohen (146), benchmarks for evaluating the importance of differences are: ES values < 0.49 are considered as small, values of 0.50 – 0.79 as medium, and values  $\geq 0.80$  are considered as large. Predicting factors were computed through multiple linear regression analyses, using the enter method. A random sample of 70 patients within CKD 5 (n=394) was extracted using a random number table.

## 5 RESULTS

### 5.1 EVALUATION OF THE IPQ-R QUESTIONNAIRE (STUDY I)

The psychometric assessments indicated evidence for construct validity of the IPQ-R in a CKD-ND context. The most supported IPQ-R dimensions were identity, timeline cyclical, consequences and emotional representations. However, the illness coherence, timeline and controllability dimensions showed less support for validity.

*Content validity:* The cognitive interviews demonstrated an overall impression of the IPQ-R items to be appraised as relevant, interesting, thought-provoking, pressing and easy to understand and respond to. The instructions and category scoring of the items were perceived as clear. The respondents expressed having difficulties connecting experienced symptoms to their CKD. Further, hesitations were expressed as to whether other disabilities or suspected effects of current medication should be regarded when responding to some of the symptom statements.

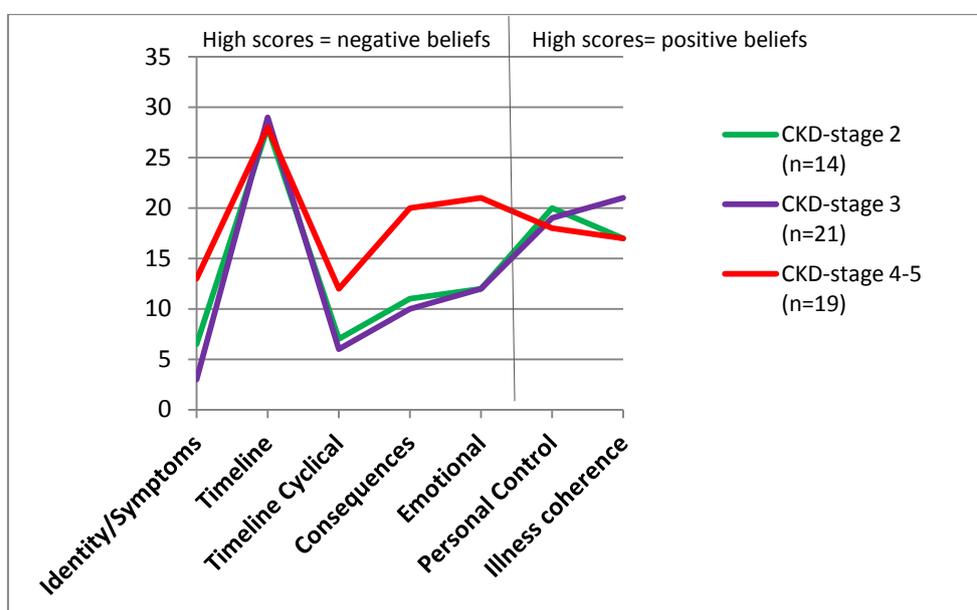
*Reliability and scale inter-correlation:* In the test for internal consistency, all dimensions had an acceptable Cronbach's  $\alpha$  above .70 except for 'treatment control', which had an unacceptable coefficient of .23 (145). Consequently, 'treatment control' was deleted for further evaluation. The test-retest showed no significant difference over time, except for the personal control dimension ( $p=.006$ ). The inter-correlations between IPQ-R dimensions demonstrated large (correlation coefficient  $>.5$ ) to moderate (correlation coefficient  $=.5-.3$ ) magnitude between 'identity', 'consequences', 'timeline cyclical' and 'emotional representations'. 'Personal control', 'illness coherence' and 'timeline' correlated only with a small (correlation coefficient  $=.3-.1$ ) to insubstantial (correlation coefficient  $<.1$ ) magnitude (146).

*Concurrent validity:* When comparing the CKD-stages and symptom burden, those in CKD-stage 4-5 and those with  $\geq 8$  symptoms held stronger beliefs about their illness as being serious ('consequences',  $p=.0001$  and  $.000$  respectively), unpredictable ('timeline cyclical',  $p=.006$  and  $.024$  respectively) and evoking emotional response ( $p=.003$  and  $.023$  respectively) than those in CKD 2 and 3 (Figure 5) and those with  $<8$  symptoms. Moreover, the patients in CKD-stage 4-5 also experienced more symptoms ('identity',  $p=.002$ ) than those in CKD 2 and 3. The patients with  $\geq 8$  symptoms also expressed less understanding of their condition ('illness coherence',  $p=.050$ ) than those with  $<8$  symptoms. The group in CKD-stage 3 perceived higher 'illness coherence' ( $p=.040$ ) than those in the other CKD-stages. The 'personal control' and 'timeline' scores did not differ significantly between the groups.

*Convergent validity:* 'Identity', 'timeline cyclical', 'consequences' and 'emotional representations' correlated negatively to impaired physical, mental and general health perceptions measured by SF-36 (range  $r: -.312 - -.773$ ,  $p <.05$ ). The correlation magnitude was moderate to large. The same four IPQ-R dimensions also correlated with a moderate magnitude to most coping styles in the JCS-60 questionnaire (range  $r: .271 - .556$ ,  $p <.05$ ). However, 'illness coherence' and 'timeline' demonstrated insubstantial to small correlations to both SF-36 and JCS-60. The patient group with  $\geq 8$  symptoms had a significantly higher use of palliative ( $p=.032$ ), supportant ( $p=.030$ ), evasive ( $p=.022$ ) and emotive ( $p=.020$ ) coping styles than those with  $<8$  symptoms. Fatalistic coping style correlated significantly ( $r=.330$   $p <.05$ ) with CKD stage, reflecting more negative IR in CKD 4-5. Personal control correlated significantly with use of confrontive ( $r=.305$ ,  $p <.05$ ) and optimistic ( $r=.271$ ,  $p <.05$ ) coping styles, and negatively with fatalistic ( $r=-.312$ ,  $p <.05$ ) coping style.

## 5.2 IR PATTERNS (STUDY I)

The median scores of all participants were relatively high on timeline (93% of maximum score), illness coherence and personal control (80% and 63% of maximum scores respectively), indicating that they assessed their condition as chronic, experienced relatively high illness coherence and had positive beliefs about the controllability of the illness. The median scores were relatively low on timeline cyclical (45% of maximum score), consequences and emotional representations (40% and 43% of maximum scores respectively), indicating that the participants did not hold as strong beliefs about the cyclical nature, negative consequences and emotional impact of the illness. A median of eight symptoms was reported. As illustrated in Figure 5, patients in earlier CKD stages perceived a different understanding of their condition than those in more advanced disease stages. The patients in earlier disease stages experienced less symptoms and did not hold as strong beliefs about the illness as being unpredictable ('timeline cyclical'), serious ('consequences') and as evoking emotional response as those on the advanced stages. Moreover, patients in advanced CKD stages or experiencing more symptoms expressed less illness coherence than those with moderately reduced kidney function or experiencing fewer symptoms.



**Figure 5. IPQ-R measures with participants divided into stages of CKD**

High scores on the left side of the dividing line indicate the illness assessed as more symptomatic, chronic, unpredictable, serious and linked to negative feelings. High scores on the right side of the dividing line represent positive beliefs about the personal controllability and understanding of the illness

## 5.3 CAUSAL ATTRIBUTIONS (STUDY I)

As shown in Table 9, heredity, chance/accident, poor medical care in past, germ/virus, altered immunity and stress/worry had the highest mean scores of the 17 proposed personal causal attribution alternatives. The patients could report more than one causal attribution. When including only those who responded 'agree' or 'strongly agree' to a causal item, 104 responses were collected. The causal attribution alternatives were collapsed into four categories: 'Accident or chance': (28% of the responses), 'Immunity' (19%), 'Heredity' (16%) and 'Behavioural and psychological attributions' (37%) as contributory cause to their CKD (Table 10). Only two of the responses in the latter category referred to alcohol and smoking.

From the interviews, two citations from the respondents expressing their thoughts regarding causal attributions are quoted here:

“.../...there's this thing where you feel guilt in some way.../...I've had quite a stressful job, and I think also my dietary habits might have had an influence” (R1)

“Well I have got information that I do have polycystic kidney disease and that it may break out, but that it need not do so if I only attend to the medical checks and take care of myself, but the illness will be much more unpredictable if I don't do this.../...Of course I know that I should not get cold and I have to think about holding my back warm enough and so on.../...I'm thinking of the summers when I was a child. Then I got cold walking along with wet swimming trunks. I could have prevented and affected the development of the disease by not doing so.../...I am also aware of that I should avoid salt and strenuous activities, but I'm quite unsure if it has any impact” (R2)

**Table 9. Distribution of item responses, causal attributions (n=52 patients)**

Causal attribution	Score, M (SD)	% agree or strongly agree
Hereditary – it runs in the family	2.9 (1.5)	33
Chance or accident	2.6 (1.3)	25
Poor medical care in my past	2.5 (1.4)	25
A germ or virus	2.4 (1.3)	19
Altered immunity	2.3 (1.4)	19
Stress or worry	2.3 (1.2)	15
Overwork	1.9 (1.2)	13
Family problems or worries	1.8 (1.0)	12
My emotional state (feeling down, lonely, anxious)	1.8 (1.1)	12
Diet or eating habits	2.1 (1.1)	10
My own behaviour	2.0 (1.0)	8
Accident or injury	1.5 (1.0)	6
My mental attitude (thinking about life negatively)	1.7 (1.0)	4
Alcohol	1.5 (0.8)	2
Smoking	1.3 (0.8)	2
Pollution in environment	1.8 (0.9)	0
My personality	1.5 (0.8)	0

Scoring range: 1= strongly disagree, 2= disagree, 3= neither agree nor disagree, 4=agree, 5= strongly agree. Respondents could choose more than one attribution (values total more than 100%).

**Table 10. Distribution of item responses, categorized causal attributions (n=104 responses)**

Categorized causal attributions	N (%) agree/strongly agree
Behavioural and psychological attributions <sup>1</sup>	38 (37)
Accident or chance <sup>2</sup>	29 (28)
Immunity <sup>3</sup>	20 (19)
Heredity	17 (16)

<sup>1</sup> 'Behavioural and psychological attributions' including own behaviour, diet/eating habits, smoking, alcohol, stress/worry, mental attitude, family problems/worries, overwork, emotional state

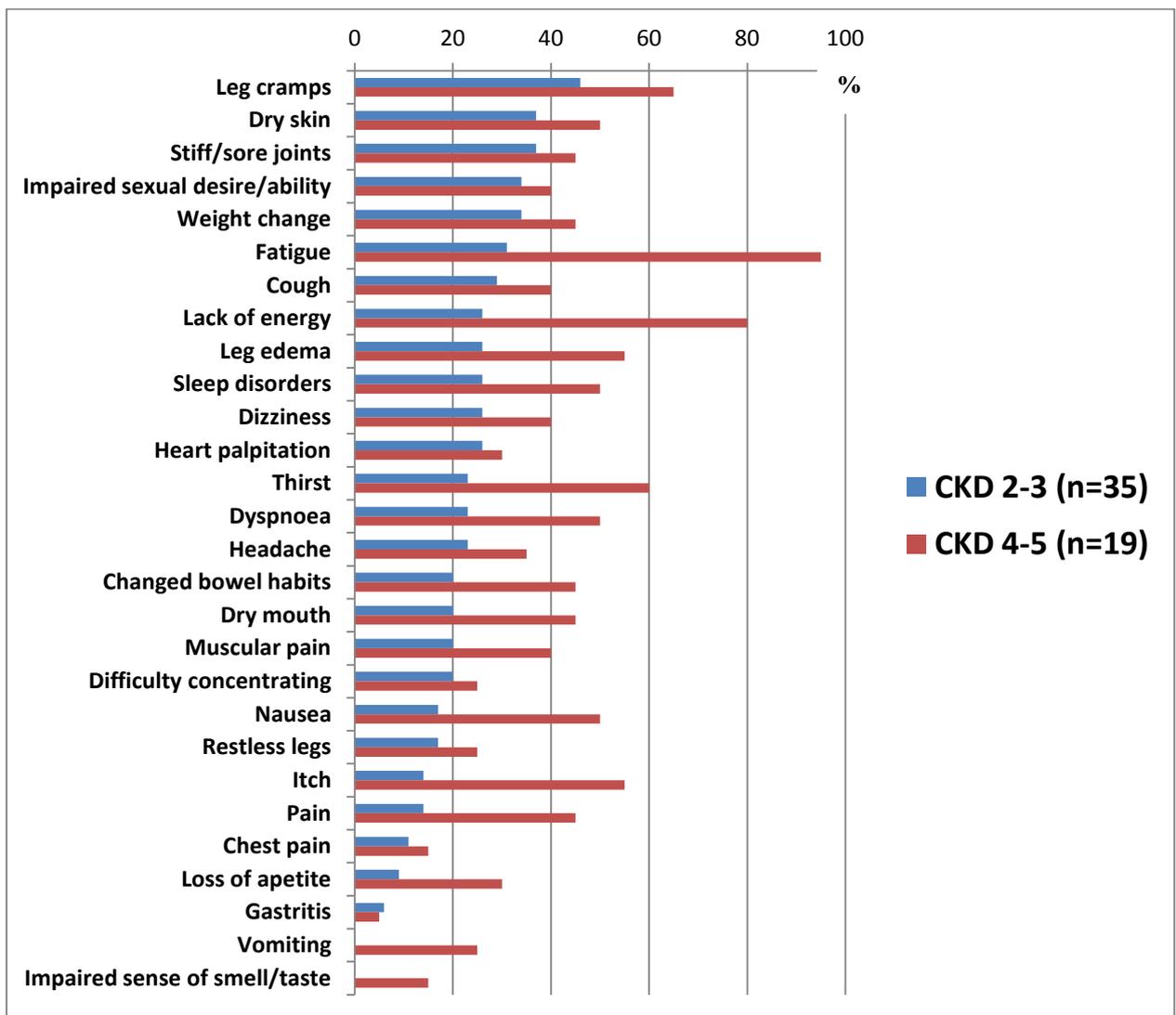
<sup>2</sup> 'Accident or chance' includes chance, accident, injury, poor medical care in past.

<sup>3</sup> 'Immunity' includes germ/virus, altered immunity

Psychological attributions (stress/worry, family problems/worries, overwork, emotional state, mental attitude) correlated significantly ( $p \leq .01$ ) to identity, timeline cyclical, consequences, emotional representations and also negatively to illness coherence.

## 5.4 SYMPTOMS (STUDY I)

In the interviews, the respondents expressed having difficulties connecting experienced symptoms to their CKD. Further, hesitations were expressed as to whether other disabilities or suspected effects of current medication should be regarded when responding to some of the symptom statements. Reported symptoms ranged from 0 - 27 (M= 8.4, Md=8). The more impaired kidney function, the more symptoms stated. The most frequently reported symptoms were fatigue and leg cramps (54% respectively), lack of energy (46%), stiff/sore joints and changed bowel habits (41% respectively), thirst, dizziness and cough (37% respectively). As seen in Figure 6, reported symptoms varied between CKD stages. The most commonly reported symptoms in CKD 2-3 were leg cramps, stiff/sore joints, dry skin, impaired sexual desire/ability and weight change. In CKD 4-5, the most common symptoms were fatigue, lack of energy, leg cramps, thirst, itch and leg edema. Eleven (58%) of the patients in CKD 4-5 and 14 (40%) of those in CKD 2-3 reported some form of pain (general pain, headache, chest pain or muscular pain).



**Figure 6. Perceived symptoms in different stages of CKD. The bars indicate percentage of patients perceiving the actual symptom.**

The patients expressed having difficulties connecting experienced symptoms to their CKD. In 68% of the symptoms reported by the patients in CKD stage 2, 44% in CKD stage 3 and 35% in CKD stage 4-5, were assessed as uncertain as to whether they were related to their kidney disease. Leg cramps, impaired sexual desire/ability and fatigue/loss of energy were the

symptoms mainly related to uncertainty. In the interviews, the respondents expressed hesitations as to whether their symptoms were related to other disabilities or to effects of current medication. One respondent stated his uncertainty as below:

*"I'm uncertain if some of the symptoms really have to do with my kidney disease. Like the diarrhea, it could as well be my diabetes or my medication. Also the muscular pain, I do have it quite often, but I don't know what it is due to. If my blood sugar is high, for example, then I get muscular pain. I also have some troubles with breathing at night. But then I don't know if it's due to the kidneys or if it's something else.../...The shortness of breath I think could be because I'm out of condition. The cough I believe is due to my earlier tracheotomy, the headache I connect to my blood sugar, the gastritis has been around since earlier, the pain in my feet I think is due to the diabetes, my sleeping difficulties I think is due to my personality and the dry skin is because I often take a shower."*(R7)

Symptoms correlated significantly (range  $r$ : .391 - .617) with negative IR, decreased HRQoL (range  $r$ : -.438 - -.670) and with evasive ( $r$ =.446), emotive ( $r$ =.419), palliative ( $r$ =.408), supportant ( $r$ =.343) and self-reliant ( $r$ =.329) coping styles. Furthermore, the patients experiencing more  $\geq 8$  symptoms expressed less illness coherence ( $p$ =.050) than those experiencing fewer ( $< 8$ ) symptoms.

## **5.5 HRQOL PATTERNS IN DIFFERENT CKD STAGES (STUDY II)**

The HRQoL scores in all dimensions impaired progressively and significantly ('bodily pain':  $p$ =.012, all other dimensions:  $p$ =.000) across kidney function levels and CKD stages, with the lowest scores in CKD 5. The largest differences between the patient groups were seen in 'physical functioning' (F-ratio=67,1) and in 'role physical' (F-ratio=64,3). The smallest disparities were seen in 'bodily pain' (F-ratio=7,1) and in 'mental health' (F-ratio=13). These smaller differences still met the criteria for minimal clinically important difference (MCID) for SF-36, i.e. of 3-5 score units (111).

The patients in CKD 2-3 (GFR range 69-31ml/min/1.73m<sup>2</sup>) had significantly lower scores on all HRQoL dimensions than the matched controls ( $p$  range: .000 - .055), with differences of large magnitude (ES 1.28 and 0.85 respectively) in 'general health' and PCS. 'Role emotional' and MCS both had ES of small magnitude ( $< 0.49$ ). All other dimensions had a medium sized ES (0.50-0.79).

The patients in CKD 4 demonstrated deteriorated scores with a large magnitude in 'physical function' (ES=1.05), 'general health' (ES=0.94) and PCS (ES=0.98) compared to those in CKD 2-3. 'Role physical' (ES=0.70), 'vitality' (ES=0.51) and 'social functioning' (ES=0.64) showed differences of medium magnitude.

The patients in CKD 5 demonstrated deteriorated scores with a medium sized magnitude in 'role emotional' (ES=0.54) and MCS (ES=0.52) compared to those in CKD 4. All other differences between these groups had small ES.

MCID was not approached in mean MCS and 'mental health' between CKD 2-3 and 4. This was also observed in mean PCS and 'general health' between CKD 4 and 5. Instead, an obvious drop in PCS was seen within CKD 3.

## **5.6 CORRELATES TO AND PREDICTORS OF IMPAIRED HRQOL (STUDY II)**

Patients with GFR  $< 45$  ml/min/1.73m<sup>2</sup> as well as CRP  $\geq 5$ mg/L, Hb  $\leq 110$ g/L and p-albumin  $\leq 35$  g/L had significantly lower scores on all HRQoL dimensions. Among the patients with CVD, the PCS and all physical subscales were significantly lower than in those with no

history of CVD ( $p < .05$ ). In the patients with diabetes, PCS and 'vitality' were significantly lower compared to those without diabetes. Patients with overweight (BMI  $>30$ ) had significantly lower scores on PCS, 'physical function' ( $p=.006$ ) and bodily pain ( $p=.041$ ) than their counterparts. However, no difference was seen between patients with BMI  $\leq 20$  compared to those with BMI  $>20$ . The group aged  $\geq 61$  years showed lower scores on PCS, 'physical function' and 'role physical' than the younger group, all at a significant level ( $p=.000$ ). MCS was not affected significantly by age, although the 'role emotional' subscale was impaired among those  $\geq 61$  years than in the younger group ( $p=.004$ ). Gender did not affect HRQoL significantly, nor did hypertension (MAP  $>110$  mmHg). All significant differences ( $p < .05$ ) met the required MCID for SF-36.

Multiple linear regression analyses were performed with the response variable 'PCS' and 'MCS' respectively. Ten explanatory variables were included: GFR, age, gender, CVD, diabetes, Hb, log CRP, p-albumin, MAP and BMI. CRP and CVD emerged as primary predictors of impaired HRQoL, followed by reduced GFR and diabetes. In the multiple regression analyses, a significant model for PCS emerged ( $F_{5,170} = 31.062$ ,  $p=.000$ ). The regression was a rather good fit; which means that 46,2% of the variance in PCS was explained by the model (Adjusted R square=.462). Five of the ten explanatory variables had a significant predictive capacity. Out of the model's explanatory variables, 'CRP' (Beta=-.279,  $p=.000$ ) and 'CVD' (Beta=-.233,  $p=.002$ ) showed the highest levels of explanation, followed by 'GFR' (Beta=.191,  $p=.003$ ), 'diabetes' (Beta=-.160,  $p=.008$ ) and 'age' (Beta=-.158,  $p=.021$ ). The variables gender, p-albumin, Hb, MAP and BMI showed no significant predictive capacity. No significant model emerged with MCS as response variable. In the final model for MCS only one of the explanatory variables demonstrated a significant predictive capacity: 'CRP' (Beta=-.271,  $p=.001$ ). The regression was a poor fit; only 11.7% of the variance in MCS was explained by the model (Adjusted R square=.117,  $F=5.626$ ,  $p=.000$ ).

## 6 DISCUSSION

### 6.1 METHODOLOGICAL CONSIDERATIONS

Some methodological aspects of this thesis ought to be considered and deserve particular attention. The participants in the studies were not randomly selected, which could increase the risk for selection bias. Further, gender distribution was somewhat skewed with a majority of males, but this is in accordance with the gender distribution in CKD patients.

In both studies, questionnaires with Likert-type scales and summated ratings have been used. All three questionnaires (IPQ-R, SF-36, JCS-60) have been found feasible and easy to accomplish, with a completion time of about 10-15 minutes each. SF-36 and JCS-60 have both previously been translated, validated and tested for use in Sweden (142, 148). Moreover, the questionnaires used in this thesis were multiple-item scales. This means that several items are addressing the same dimension of a construct, and are summated to a dimension score. This design improves the reliability and averages out random errors and internal dropouts (149).

However, when using Likert-type scales one has to consider methodological issues and sources of bias such as central tendency bias (respondents tend to avoid extreme response alternatives), acquiescence bias (respondents tend to agree with the statements) and social desirability bias (respondents tend to answer in a manner that will be viewed favorably by others). Moreover, the respondent may misinterpret an item, respond in a biased way, or by mistake pick the incorrect response alternative. The design and wording of the introduction to a questionnaire is important. The researchers must make sure that the respondents understand the purpose of and the instructions to the questionnaire before use. Therefore, cognitive processes need to be considered, which was also accomplished in study I.

When transforming raw scores to derived scores, we used the appropriate scoring manual and syntax for each questionnaire. The derived scores may be difficult to interpret, for example what does a value of '40' on 'general health' in SF-36 mean? One way of facilitating the interpretation is comparing data with previous research results and with results from a reference population. Another important aspect of interpreting derived scores is to assess the clinical relevance of the measured differences between groups or occasions. A statistically significant change does not necessarily imply any difference of clinical importance.

Likert-type scales are used in order to capture the variation of the phenomenon or attitude of interest. The response alternative format is on an ordinal level, for example rating an item as '*strongly disagree*', '*disagree*', '*neither agree nor disagree*', '*agree*' or '*strongly agree*'. However, the items are weighted equally and graded as interval level data. This has been discussed in literature, with considerable disagreement. While some argue that for ordinal data non-parametric statistics should be employed (150), others insist that Likert data can be considered as robust and be analyzed through parametric statistics (151). When handling data, this should be considered.

With this said, the advantages of a validated questionnaire, such as being timesaving, convenient and considered to deliver robust data (151) merits attention.

#### 6.1.1 Study I

Regarding the psychometric testing of IPQ-R, the self-reporting method by mail is limited by the respondent's ability to read and comprehend the questions/statements and has a higher risk for non-response bias, even though it is considered as convenient and conventional (152). On the other hand research has shown that surveys with low response rates can be more

accurate than surveys with higher response rates (153). Also, one has to consider that despite thorough information regarding the study was sent to the participants together with the questionnaires, consent form and contact information, the opportunity for the participants to ask questions can be conceived as more dissociated with this conduct. This may explain some of the drop-outs. More demographic data on the participants might have revealed a possible correlation between for example illness coherence and educational level. Research within health psychology has demonstrated that demographic factors do have an impact on IR and coping (50), and that individuals with a higher educational level are more likely to holding beliefs compatible with the scientific medical approach and a preventive view of health (154). The psychometric assessments were conducted in order to accumulate evidence for validity and reliability. In this, the testing procedures used by the developers of the IPQ-R were followed, which can be favourable from a comparing point of view. On the other hand, it could have been more explorative to complete the evaluation by using alternative methods according to the item response theory (modern mental test theory) (155). The number of 54 participants in the psychometric assessments precluded the possibility to run factor analyses and further evaluation of the causal dimension. However, the sample size was estimated to about 50 participants. This estimation did not include any factor analysis, which would request at least 200 participants or 5-10 participants per variable (156). Due to a potential type II error ('false negative' outcome), it is possible that a larger sample size could have enabled the identification of more and stronger relationships with SF-36 and JCS-60.

Considering the demography in the cognitive interviews of the IPQ-R evaluation, a majority of the subjects had a university educational level. This is probably not a representative distribution. They might have been more comfortable with the proposed wording as well as reading and responding to a questionnaire. Moreover, the respondents were younger than patients with CKD in general, but this ought not to be a factor that influences the usability outcome. The fact that the interviewer also belonged to the staff of the current clinic may compose a bias risk, considering that a dependent situation for the respondent may affect the responses. This may imply a risk for central tendency bias as well as acquiescence bias and social desirability bias. It should be stressed that cognitive interviewing does not validate a questionnaire in a formal sense like statistical proofs (133) but is more a test of content validity and usability (157). Nevertheless, the use of cognitive interviews in this study comprises an advantage as it retrieves direct information from the participants and covers important cognitive respondent aspects, which minimizes the risk for misinterpretations and uncertainties. This improves the psychometric evaluation process of a questionnaire design.

### **6.1.2 Study II**

In study II, the group sizes of patients in different CKD stages and GFR levels were disproportionate, with most participants in CKD 5. This, as well as the context for this study setting, has to be considered when interpreting the results. However, the multiple regression analyses were performed with proportional group sizes. Unfortunately, the study did not cover patients in GFR levels between 31-50 ml/min/1.73m<sup>2</sup>, but indicated that this GFR span may embed a turning point for a pronounced drop in PCS.

Moreover, a cross-sectional design is limited by only providing a snapshot and its difficulties to make causal inference. Thus the evolution of the participants' HRQoL was not followed over time in this study, which may be of importance when interpreting the illness trajectory. Follow-up studies on HRQoL are still rare. Therefore, this should be focused on in future research.

Other potential sources of error are misclassification (information bias) and confounding. For example, it is possible that symptoms and comorbidity may be unrecorded and thus

underestimated. Potential confounding factors were adjusted in the regression model. Still, influence of comorbidity remains a possible bias.

When interpreting a HRQoL instrument, one has to consider its limitations. Ceiling and floor effects may skew the results. The individuals' assessments of their health status are strongly subjective and affected by surrounding factors like cultural aspects and environmental changes, which should be taken into account when interpreting and comparing results of HRQoL (158). Furthermore, the response shift phenomenon, i.e. the patients' adaption to or recalibration of their health condition may have influenced the individual responses in this study (159). One can also presume that the patient's awareness of the diagnosis or 'labelling' phenomenon may influence the individual's health perception in asymptomatic conditions (112). In this study solely biological variables were collected for correlation analyses. This has to be kept in mind when drawing conclusions. If non-biological variables (such as psycho-social aspects, illness representations, sense of coherence, locus of control, self-efficacy, coping strategies and self-management) had been assessed, this might have contributed to a more holistic perspective of components correlating to and predicting HRQoL – especially the mental domains - in this patient group. Moreover, one has to consider that the SF-36 does not capture all dimensions that may be included in HRQoL for patients with CKD, such as for example sleep, sexual and cognitive functioning.

Advantages of this study are the large number of patients, in particular in CKD 5, which has not been well studied previously regarding HRQoL. The study provides insights into the changes in HRQoL throughout the CKD trajectory, and contributes to increased knowledge regarding HRQoL in earlier CKD stages as well as in advanced CKD and at initiations of dialysis treatment. It also highlights the relationship between HRQoL and inflammation and CVD in this patient group.

## **6.2 FINDINGS AND INTERPRETATIONS**

### **6.2.1 Evaluation of the IPQ-R Questionnaire**

The psychometric evaluation indicated evidence for construct validity of the IPQ-R in a CKD context. Satisfactory usability and content validity were demonstrated. 'Identity', 'timeline cyclical', 'consequences' and 'emotional representations' were the most supported dimensions. These findings seem consistent, as it can be assumed that with presence of more symptoms the illness (i.e. CKD) would be perceived as unpredictable, serious and evoking emotional response. Experiencing more symptoms and perceiving CKD as more threatening was associated with an impaired HRQoL and also with mainly evasive, fatalistic, emotive and supportant coping styles. This indicates an interrelationship between IR and HRQoL, and that they have an impact on health-related behaviour. This is also confirmed by others (1).

The illness coherence, personal control and timeline dimensions did however show less evidence for validity. Hence they seem not to be appropriately covered by the construct in this context and thus need to be further explored in this patient group. A possible explanation to this could be that illness coherence may not trigger to coping behaviour or health reflections like symptoms do. A person carrying a chronic disease struggles to "normalize" the condition and incorporate it into daily life – a process that may pose a risk for avoidance of further reflections, which has been described in a phenomenological study on falling ill with diabetes (160). This could be one explanation to the relative decrease of illness coherence as the disease progresses, which was indicated in present results. A weak relationship to 'illness coherence' in HD patients has also been found by others (89), indicating that this dimension should be interpreted with care in renal patients.

The treatment control dimension did not demonstrate internal consistency in this context. A possible explanation could be that the items within treatment control dimension seem to not suit this patient group and the CKD trajectory. On the other hand, treatment control perceptions have been shown to predict survival in dialysis patients (91). Regarding 'personal control', the significant correlations with confrontive and optimistic copings styles confirm the theory of locus of control (i.e. a person's perceived control over his or her own behaviour) (53). On the other hand, the small magnitude of correlations found between 'personal control' and SF-36 needs to be further explored, since it is opposite to the idea that personal control enhances psychosocial HRQoL (161). Moreover, the personal control dimension indicated instability in the test-retest, which should be considered when aiming to identify temporal changes. This instability over time has been indicated earlier in renal patients (65). It may reflect that the personal control dimension could be interpreted as broad and complex (129). On the other hand, the lower ratings on 'personal control' in the retest could reflect a reactive effect of the first test, embracing an understanding leading to a reappraisal of control efficacy and how one actually manages the illness. This was also indicated in the cognitive interviews, where the questionnaire was appraised as thought-provoking. Research suggests that the individual's IR can be changed, offering opportunities to improve the patient's adjustment to his illness (57). Previous research has also demonstrated factorial hesitations regarding the controllability dimensions (87). As pointed out by these authors, an understanding of patients' beliefs in the control of their conditions is indeed essential to support and empower self-management in chronic diseases. Furthermore, it can be assumed that with vague and/or few symptoms, the individual has a lower level of disease awareness. Hence IPQ-R used in a CKD 2-3 context should be interpreted with care and with respect to symptoms and disease burden.

### **6.2.2 IR in CDK patients**

IR differed with CKD stages, and the patients in earlier disease stages did not hold as strong beliefs about the illness as being as threatening (i.e. unpredictable, serious and as evoking emotional response) as those on the advanced stages. One explanation to these differences could be that few and insidious symptoms may imply few cues to - and awareness of -the illness, implying uncertainty regarding its course, severity and management. According to the CSM, 'identity' (symptoms) is considered as a core dimension and a starting point for the parallel process of emotional and cognitive responses and coping in the model. Difficulties in connecting experienced symptoms to CKD were found, and common symptoms related to uncertainty were leg cramps, impaired sexual desire/ability and fatigue/loss of energy. Besides from experiencing more or less insidious symptoms related to renal insufficiency, persons with CKD often suffer from comorbidities. It was also pointed out in the interviews that it can be difficult to assess if symptoms are caused by other conditions or by side effects of the medical treatment. This uncertainty of tracing symptoms was also observed in a validation of IPQ-R among patients with cancer (86), and is an important finding since uncertainty of symptoms has been shown to associate to decreased adherence to prescribed treatment (162, 163). Furthermore, the results indicated that the patients experiencing more symptoms or in advanced CKD stages expressed less illness coherence than those experiencing fewer symptoms or with moderately reduced kidney function. It is plausible that experiences of diffuse and various symptoms may imply less sense of control and illness coherence. Interestingly, our findings also indicated that several symptoms were experienced already in CKD 2-3, such as leg cramps, stiff/sore joints, dry skin and impaired sexual desire/ability. This is surprising, since CKD stages 1-3 are considered to be asymptomatic, and these symptoms commonly are observed in advanced CKD or ESRD (13, 164). Within the health psychology field, it is acknowledged that even though an illness may be asymptomatic, being given a diagnosis affects the patient to search for symptoms (57). However, certain health-related manifestations may not be recognized by the renal team due

to lack of attention to these symptoms. On the other hand, the patients may be reluctant to report symptoms they perceive as unimportant, untreatable or irrelevant to their CKD.

When collapsing the causal attributions into four categories, a substantial part of the responses referred to 'behavioural and psychological attributions' as a contributory cause to their kidney disease, i.e. diet, stress/worry, mental attitude, family problems/worries, overwork and emotional state. However, very few referred to smoking or alcohol as a contributing cause. This contradicts research within CVD care, where smoking has been a frequently attributed cause to the illness (165, 166). The referral to behavioural attributions was also confirmed in the interviews, where some patients expressed thoughts about self-blame and an uncertainty whether they had neglected their health. Furthermore, psychological attributions correlated to negative IR and to less personal understanding of the illness. In previous research, self-blame has been identified as a common causal attribution, and described as strongly influencing other IR dimensions and coping (57, 59).

### **6.2.3 HRQoL in CKD patients**

The findings indicate significantly impaired HRQoL across CKD stages. As expected, the lowest HRQoL scores were seen in the patients with the most declined kidney function, substantially deviating from the Swedish reference population (139). The decline in HRQoL with deteriorating kidney function is congruent with previous findings (124). The mean scores of the patients in CKD 5 (of which 80% were initiating dialysis treatment) were lower than among those in a Dutch study where HRQoL was assessed 0-4 weeks prior to dialysis initiation (127). This confirms the continuous deterioration of HRQoL with more advanced disease stages. Current findings indicate that the patients in CKD 5 showed even worse HRQoL scores than previous assessments in several dialysis populations (167), suggesting that this period of the disease trajectory may be exceptionally vulnerable. The time period right before and at initiating dialysis treatment can be described as a transitional state, where the situation often appears as fragile and uncertain to the patient. In addition to a decline in physical health, stress, anxiety and depression often occur in the period preceding dialysis initiation (168-170). It is therefore reasonable that also the mental dimensions should be reflected in HRQoL assessed at this point. Stress, emotional distress and impaired HRQoL have been described as associated with health-illness transitions, and the nurse's assignment to identify critical points during transitions for preventive measures such as educational and supporting interventions have been suggested as important (48, 49).

The results showed that CKD has a negative impact on HRQoL – especially in the physical function and role domains - already in earlier stages of the disease. These results are in line with findings in previous studies (114, 124, 126). The patients in CKD 2-3 (with GFR range 69-31 ml/min/1.73m<sup>2</sup>) scored significantly lower than the controls in all HRQoL dimensions, with the largest differences shown in physical health. The scores were also lower compared to the Swedish reference population (139). This indicates that CKD even at an early stage seems to imply restrictions in daily life, though it has been considered not to impact the individual's health experience.

The associations between factors such as GFR, CVD, diabetes, age, decreased Hb- and p-albumin levels and impaired HRQoL shown in this thesis might be expected and are congruent with previous findings (114, 124). However, the GFR level did not – as assumed - show any prominent predictive capacity in the multiple regression analyses. Interestingly our results instead demonstrated that inflammation and CVD seem to be primary predictors of impaired HRQoL in patients with CKD, followed by reduced GFR and diabetes, meaning that the patient's health perception is not only related to the kidney function level, but also to other conditions - like inflammation, CVD and diabetes. Moreover, the results

indicate that a relatively moderate increase in CRP may affect HRQoL. These findings highlight that key elements concerning HRQoL in CKD patients are still not settled and indicate that more attention should be paid to conditions such as inflammation and CVD. To our knowledge, the relationship between inflammation and HRQoL in this patient group is still not very well documented. It has previously been demonstrated that increased levels of inflammation related cytokines are associated with deteriorated self-rated health (171). Our results showed elevated CRP levels across the CKD stages, where occurrence of CRP >5mg/L increased with declining kidney function. This is in line with previous findings (22, 26) and the presumption of a chronic low-grade inflammation process, starting already in early CKD stages (23). Besides being an inflammation marker, CRP has also been pointed out as a strong predictor of CVD events (21, 172). Moreover, and congruent with previous research (173, 174), about half of the patients had a history of CVD, and about a third had diabetes. Conditions like inflammation, CVD and diabetes often appear in CKD patients, share both risk factors and some symptoms, and have a negative impact on HRQoL. By screening for these already from an early stage, the possibility for treatment and secondary prevention may increase and contribute to improved well-being and function.

Research within renal care (114, 124), in other conditions like chronic heart failure (175) and also in the Swedish reference population (139) have demonstrated women reporting worse HRQoL than did the men. However, no association was found between HRQoL and gender in our results. This finding was identified even though a history of CVD and higher CRP-levels were more common among males.

Large impairments in physical health across the CKD stages were found in this thesis. The patients in CKD 4 had impaired scores in 'physical function', 'general health' and PCS compared to those in earlier disease stages. The decline in 'vitality' indicates that the deteriorated physical function may be connected with symptoms like lack of energy, feeling tired and worn out, which are embraced in the 'vitality' concept. Fatigue/feeling tired and lack of energy have emerged as the most commonly reported symptoms in CKD 4-5 (176). Moreover, it is well known that patients with advanced CKD have reduced physical functioning and performance (177, 178), that this is linked to fatigue (179) and that inactivity has an impact on fatigue in HD patients (180). Our results confirm previous findings that GFR around 45 ml/min/1.73m<sup>2</sup> seem to be a dividing line for drop in HRQoL, especially in physical health (114). It also supports the hypothesis of a turning point in physical health at a relatively early and 'asymptomatic' stage. This is further confirmed by others who have found physical fitness and functioning to be reduced already in earlier CKD stages to approximately 70% of the expected norm (177). The loss of physical fitness and function demonstrated in this and other studies is alarming and has to be addressed already at a mildly diminished kidney function. Enhanced physical activity and exercise training programmes to patients with renal insufficiency have been highlighted as interventions improving HRQoL (110, 177). Furthermore, resistance training has been proposed as a beneficial strategy also from an inflammation perspective (21, 181) and CVD (25, 182). Other interventions to enhance HRQoL in CKD patients, such as therapy optimization, management of anaemia, sleep disturbances, depression, stress and anxiety and support in cognitive dysfunction have been suggested (110). Having a comprehensive approach has also been highlighted as important (112).

#### **6.2.4 IR, HRQoL and self-management**

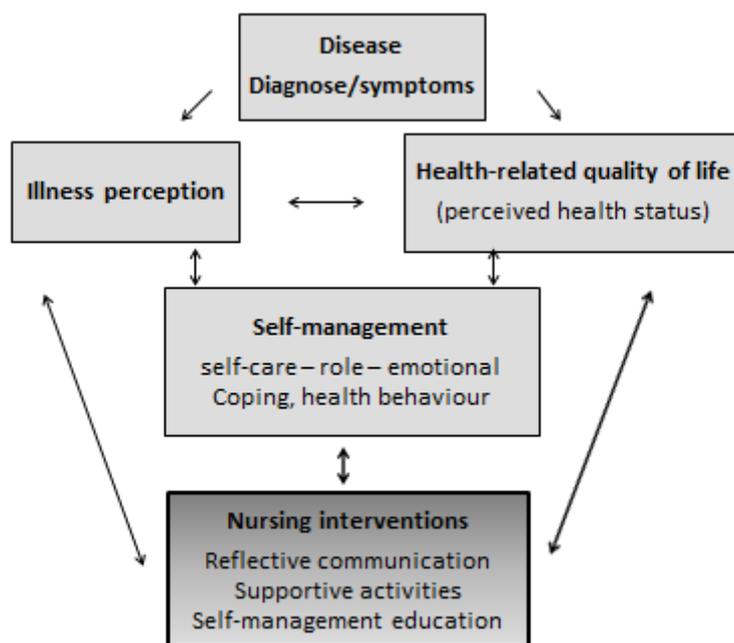
This thesis aimed at exploring IR and HRQoL in different stages of CKD up to initiation of dialysis treatment. In accordance with previous research, a relationship between IR and HRQoL and health behaviour was assumed. The results showed that symptoms and IR

correlated with decreased HRQoL and also with mainly evasive, fatalistic, emotive and supportant coping styles. Simply knowing that one's disease as incurable affects HRQoL negatively (183). On the other hand, different conditions are linked to different threat levels, where cancer and CVD represent "hot cognition", i.e. defining them as tightly linked with overwhelming fear (184). Our results indicated that the patients in CKD 2-3 did not hold as strong beliefs about their illness as being threatening. This may impact the individual's motivation to engage in medication use and life-style activities on a daily basis (185). Few and insidious symptoms may imply few cues to disease awareness, which may affect the individual's self-management and understanding of long-term consequences. Control in chronic disease is dependent on successful integration of both the medical treatment and the patient's ability to self-management (186). The decision to follow treatment recommendations will be influenced by the patient's IR and whether the treatment is perceived as appropriate (76, 187). Recently, a study revealed relatively low levels of perceived knowledge of CKD among patients treated by nephrology specialists (188). The process of becoming 'aware' of early CKD with absence of symptoms has also been highlighted in a study suggesting a model encompassing the two concepts '*discovering kidney disease*' (searching for evidence to confirm diagnosis) and '*learning to life with kidney disease*' (manage the illness, take care of oneself and need for disease-specific information) (163). Obviously, successful disease outcome is linked to successful self-management, where enhancing the patient's health literacy is crucial. Furthermore, our results showed that the patients expressed having difficulties connecting experienced symptoms to their CKD. This was applicable in the majority of the symptoms reported by the patients in CKD 2-3. Moreover, the interviews revealed an uncertainty as to whether symptoms were related to other disabilities or to effects of current medication. Given that uncertainty of symptoms is associated to decreased adherence to prescribed treatment (162, 163), this is an important issue concerning self-management, that needs to be further explored. Self-care agency and self-efficacy is considered to associate with improved HRQoL (189, 190), and impaired HRQoL may infringe on the patient's self-care agency. In this thesis, progressively impaired HRQoL across kidney function levels was found, which may affect the patients' IR and self-management. Except for providing an appropriate organization to promote self-management, this implies that also attention to the patients' HRQoL is essential for health providers intending to support self-management and to encourage dialysis treatment with a self-care modality (i.e. PD, self HD, or home HD).

### **6.2.5 Clinical nursing practice**

In renal care, it is crucial that the patient – independently of CKD-stage - comprehends his/her situation, copes in a constructive way, agrees and adheres to essential treatment and life style alterations. Exploring the patient's mind-set and HRQoL provides an important basis for understanding and supporting his/her resources and adjustment to the disease. When discussing IR and HRQoL in a chronic condition like CKD, nursing interventions, such as reflective communication, supportive activities, and educational assignments are essential. In Figure 7, the relations between IR, HRQoL and self-management outlined in Figure 3, are complemented with proposed nursing interventions. A renal care program that takes the patient's individual IR into consideration might enable nurses and the health care team to explore the patients' 'language of symptoms', thoughts of possible causes and the course of the disease in order to create an opportunity for discussion and education. This could provide a chance to address uncertainty, concerns and possible misconceptions and to identify patients at risk for sub-optimal self-management and/or impaired HRQoL, and then carry out educational interventions to support a healthy behaviour and optimal self-management (191). From a nursing perspective, retaining or increasing HRQoL and well-being constitutes a care goal (99). The most affected HRQoL dimensions – perceptions of general health and physical health - insist that recognition and management of them should be attended. HRQoL in CKD

patients may benefit from interventions such as encouraging physical activity and participation in exercise training programmes. In advanced CKD, it is pressing to highlight the vulnerable transitional situation and give proper psychosocial support to patients about to commence dialysis treatment. Attempts to enhance attitudes to dialysis treatment may improve depression and HRQoL. An improved patient – caregiver communication and a more comprehensive understanding of the patients’ perspective may be facilitated by attention to and discussion of his/her IR and HRQoL. This may compose a base for supporting and improving the patients’ self-efficacy (192) and psychosocial well-being (193). It would not only provide a tool to screen for and prioritize problems, but also highlight health promoting and illness persistent resources (i.e. what is well-functioning in the patient’s everyday life with the disease).



*Figure 7. Outline of interrelationships between illness representations, health-related quality of life, self-management and nursing interventions.*

### 6.2.6 Clinical implications and future research

In renal care, increased understanding of IR and HRQoL are important assignments, since they interrelate and also have an impact on the patients’ coping and health behaviour. Skilled attention to the patients’ IR and HRQoL may enable health care providers to identify patients at risk for sub-optimal self-management and/or impaired HRQoL, identify and focus on relevant problems as well as supporting healthy behaviour, self-management and self-care modalities of dialysis treatment.

Little is still known regarding IR and HRQoL in this patient group, why more research – preferably with qualitative as well as interventional approach - is necessary on these issues. A future pathway would be to study HRQoL in relation to non-biological variables, such as psycho-social aspects, illness representations, sense of coherence, locus of control, self-efficacy, coping strategies and self-management. Systematic assessments and follow-up of IR as well as HRQoL already from earlier CKD stages could be a useful tool, which may facilitate the communication with the patient and provide a broader understanding of the patient’s perspective. A more comprehensive approach would also take co-existing conditions such as inflammation, CVD and diabetes into account. Exploring the individual

IR and HRQoL together with the patient may be helpful in guiding use of coping- and self-management strategies. Attention to the patients' HRQoL could facilitate accomplishing individually tailored interventions to enhance or maintain his/her physical fitness/function and psychosocial well-being. Interventions aiming at giving feedback and discussing the HRQoL outcomes face-to-face with the individual patient have been studied within oncology and diabetes care (192, 193), and has also been suggested as a future pathway within renal care (194). In earlier CKD stages this kind of reflective discussions with focus on IR and HRQoL may enhance the patient's awareness of the disease and possible self-management strategies. This may help the patient to timely find healthy coping and optimal self-management strategies. Interventions of this kind might also be a helpful component in the psychosocial support required in the transitional period at the time for initiating dialysis treatment.

Moreover, there is a need to further evaluate effective interventional strategies to improve HRQoL in CKD patients, including secondary prevention of risk factors and comorbidities, programmes for improved physical activity and educational interventions. This could comprise measures and follow-up for e.g. blood pressure and blood glucose, dietary habits, oral health, weight and nutritional status, infection sites and lifestyle aspects like stress, smoking and physical inactivity.

Another research area within self-management would be adherence to medication among kidney transplant patients and in patients with advanced CKD who have a high-pill burden. Furthermore, IR, HRQoL and coping within different cultural and ethnic patient groups would be an interesting and pressing future assignment.

## 7 CONCLUSIONS

- The translated and adapted IPQ-R version in a CKD context demonstrated evidence for construct validity, but needs to be further examined regarding the illness coherence and controllability dimensions in this context.
- Illness perceptions differed with CKD stages and symptom burden. The patients in earlier disease stages or with fewer symptoms did not hold as strong beliefs about their illness as being a threat as those in advanced stages or with more symptoms.
- IR related to HRQoL. Negative IR was associated with an impaired HRQoL and with mainly evasive, fatalistic, emotive and supportant coping styles.
- Difficulties for the patients in connecting experienced symptoms to CKD elucidate a gap in patient disease knowledge, especially in earlier CKD stages.
- HRQoL scores impaired progressively and significantly already from earlier CKD stages and across kidney function levels, particularly in physical health. At the time for dialysis initiation HRQoL was substantially deteriorated.
- Impaired HRQoL scores were associated with inflammation, CVD, diabetes, decreased GFR, old age, overweight and reduced Hb- and p-albumin levels.
- Inflammation and CVD seem to be primary predictors of impaired HRQoL in patients with CKD.

## 8 SVENSK SAMMANFATTNING (SWEDISH SUMMARY)

### BAKGRUND

Kronisk njursvikt förekommer hos ca 10% av den vuxna befolkningen, med glomerulonefrit och diabetes som två ledande njursviktsorsakande diagnoser. Sjukdomen är oftast progredierande, vilket medför tilltagande rubbningar som anemi, hypertoni, inflammation, malnutrition, metaboliska störningar och bensjukdom. Tidigare njursviktsstadier<sup>1</sup> är oftast asymtomatiska, men med mer avancerad njursvikt framträder alltfler symtom, som exempelvis trötthet, illamående, försämrad aptit, törst, myrkrypningar, kramper, klåda, sömnstörningar, kognitiv påverkan och depression. Personer med kronisk njursvikt lider ofta också av andra sjukdomar och komplikationer, som t.ex. kronisk inflammation, hjärtkärlsjukdom och diabetes. Hjärtkärlsjukdom är den vanligaste dödsorsaken bland njursjuka. I tidiga sjukdomsstadier baseras behandlingen på blodtryckskontroll och andra riskfaktorer, som proteinuri, lipidrubbningar, metaboliska rubbningar och livsstilsrelaterade faktorer som rökning och fysisk aktivitet. Syftet med behandlingsregimen vid alla njursviktsstadier är att bromsa fortsatt sjukdomsprogression samt förhindra komplikationer. I detta arbete är patienten själv en viktig aktör, och individens delaktighet och egenvårdsförmåga kan ha en avgörande betydelse för dennes hälsa. För optimal egenvård är ofta flera yrkeskategorier inblandade och patientundervisning och egenvårdsstöd är viktiga delar av njursjukvård. När njurfunktionen är så pass låg att aktiv uremivård – dialys eller transplantation – måste påbörjas, innebär detta ofta en stor omställning för patienten, med en livslång behandling, som innefattar mer eller mindre av egenvård.

Då bot sällan finns utgör ökad eller bibehållen hälsorelaterad livskvalitet - dvs. fysisk, psykisk och socialt funktion och välbefinnande - ett viktigt mål i njursjukvården. Forskning visar att coping, hälsobeteende och egenvård påverkas av individens sjukdomsuppfattning och av hur individen upplever sin hälsorelaterade livskvalitet (HRQoL). Tidigare forskning inom njursjukvård visar att sjukdomsuppfattning kan ha betydelse för depression, välbefinnande, HRQoL och överlevnad samt hälsobeteende och egenvård.

Sjukdomsuppfattning handlar om individens personliga bild av sjukdomen, vilket skapas av tankar och känslor. Individen formar sin sjukdomsuppfattning dels utifrån en tolkning av sina symtom, dels utifrån en personlig tolkning av sin diagnos, baserad på information från sjukvården, men även från massmedia, vänner, familj osv. Individens coping och hälsorelaterade agerande utgår från sjukdomsuppfattningen. Frågeformuläret Revised Illness Perception Questionnaire (IPQ-R) ställer frågor om sjukdomsspecifika symtom, om man ser sjukdomen som kronisk/akut, oförutsägbar, allvarlig, om man upplever sig ha kontroll över sjukdomen, hur man ser på behandlingen, tänkbara orsaker till sjukdomen, känslomässiga reaktioner samt personlig sjukdomsförståelse.

<sup>1</sup> Njursviktsstadium	Njurfunktion glomerulär filtrationshastighet (GFR)
1. Njurskada utan påverkan på njurfunktionen	≥90 ml/min/1.73m <sup>2</sup>
2. Lätt nedsatt njurfunktion	60-89 ml/min/1.73m <sup>2</sup>
3a. Måttligt nedsatt njurfunktion	45-59 ml/min/1.73m <sup>2</sup>
3b.	30-44 ml/min/1.73m <sup>2</sup>
4. Svår njursvikt	15-29 ml/min/1.73m <sup>2</sup>
5. Mycket svår njursvikt	<15 ml/min/1.73m <sup>2</sup>

Denna avhandling fokuserar på sjukdomsuppfattning och HRQoL hos njursjuka och huvudsyftet var att utvärdera, dvs. testa de psykometriska egenskaperna avseende en till svenska översatt och till njursjuka anpassad version av IPQ-R. Vidare syftade avhandlingen till utforska sjukdomsuppfattningar och HRQoL hos patienter i olika skeden njursvikt (stadium 2-5).

## **DELTAGARE**

Deltagarna i denna avhandlings delarbeten var personer från de båda forskningsprojekten PROGRESS och PAUS samt patienter från Njurmedicinska mottagningen, Karolinska Universitetssjukhuset, Solna. Totalt deltog 596 patienter och 55 kontroller. I delarbete I deltog 7+54 patienter i CKD stadium 2-5. I delarbete II deltog 535 patienter i CKD stadium 2-5 samt 55 kontroller.

## **METODER**

Avhandlingen bygger på två delarbeten. I **delarbete I** undersöktes begreppsvaliditet gällande IPQ-R genom kognitiva intervjuer (N=7) och psykometriska test (N=54). I intervjuerna fick patienterna enligt ett särskilt testprotokoll svara på hur de uppfattade frågeformuläret och hur de tänkte när de kom fram till sina svar. Vid de psykometriska testen besvarade deltagarna IPQ-R samtidigt med enkäter om HRQoL (SF-36) och coping (JCS-60) brevledes. De fick även besvara IPQ-R ytterligare en gång (test-retest) ca 2 veckor senare. **Delarbete II** var en tvärsnittsstudie där 535 patienter och 55 kontroller deltog. Dessa besvarade enkäten SF-36 rörande HRQoL i samband med besök vid Njurmedicinska kliniken. Svaren analyserades tillsammans med biomarkörer som njurfunktion, blodtryck, vikt, förekomst av hjärtkärlsjukdom, diabetes, C-reaktivt protein (CRP) hemoglobin (Hb) och p-albumin.

## **RESULTAT**

**Delarbete I:** Resultaten gav stöd för begreppsvaliditet gällande IPQ-R i denna patientgrupp, fr.a. i dimensionerna identitet/symtom, cyklicitet, konsekvenser och emotionell respons. Svagare belägg för validitet indikerades i dimensionerna tidslinje, kontroll och sjukdomsförståelse, varför dessa bör utforskas ytterligare i denna patientgrupp. De kognitiva intervjuerna indikerade tillfredställande användbarhet och innehållsvaliditet. Sjukdomsuppfattningen varierade mellan patienter i olika njursviktsstadier och med olika symtombörda. Patienterna med lindrigare njursvikt (stadium 2-3) samt patienterna med <8 symtom hade inte lika negativ sjukdomsuppfattning som de med avancerad njursvikt (stadium 4-5) och de med  $\geq 8$  symtom. Patienterna med avancerad njursvikt och de med  $\geq 8$  symtom uttryckte även mindre grad av sjukdomsförståelse än de med färre (<8) symtom och/eller i lindrigare njursviktsstadier (stadium 3). Negativa sjukdomsuppfattningar (upplevelse av mer symtom och uppfattning av njursvikten som mer hotande) var korrelerat till försämrad HRQoL och även till framförallt undvikande, fatalistiska, känslomässiga och stödjande coping-strategier. En betydande andel av patientsvaren hänvisade till eget beteende och psykologiska aspekter som bidragande orsaker till sin njursjukdom. Respondenterna i intervjuerna uttryckte svårigheter med att koppla upplevda symtom till sin njursvikt eller om de hade med andra sjukdomar/tillstånd eller biverkningar att göra. Denna osäkerhet kring upplevda symtom framkom även i de psykometriska testen. Benkramper, hudtorrhet, ledbesvär och nedsatt sexuell lust/förmåga var vanligt förekommande symtom i CKD stadium 2-3. Denna patientgrupp uttryckte även mest osäkerhet gällande bedömning om deras symtom var kopplade till njursjukdomen. De vanligast upplevda symtomen i CKD 4-5 var påtaglig trötthet, kraftlöshet, benkramper och törst.

**Delarbete II:** Samtliga HRQoL-dimensioner försämrades signifikant med alltmer nedsatt njurfunktion, med sämst värden i njursviktsstadium 5. De största skillnaderna mellan olika njursviktsstadier sågs inom fysisk hälsa (fysisk funktion/rollfunktion). De minsta skillnaderna

sågs inom smärta och mental hälsa. Patienterna i njursviktsstadium 2-3 hade signifikant sämre HRQoL jämfört med matchade kontroller, patienterna i stadium 4 respektive 5 hade ytterligare försämrade värden. I stadium 5 kunde även försämrade mental hälsa (fr.a. emotionell rollfunktion) påvisas, jämfört med stadium 4. Glomerulär filtrationshastighet (GFR) <45 ml/min/1.73 m<sup>2</sup>, ålder ≥61 år, förekomst av hjärtsjukdom, diabetes, CRP ≥5 mg/L, Hb ≤110 g/L, p-albumin ≤35 g/L och övervikt korrelerade till försämrat HRQoL. CRP och hjärtsjukdom framstod som de viktigaste faktorerna som ökar risken för sämre HRQoL, följt av minskat GFR och diabetes.

## SLUTSATSER

- Den till svenska översatta och till njursjukdom anpassade versionen av IPQ-R befanns ha stöd för begreppsvaliditet. IPQ-R kan vara användbar inom forskning och klinisk verksamhet, men bör utforskas vidare i denna kontext.
- Sjukdomsuppfattningarna varierade mellan olika njursviktsstadier och beroende på symtombörda. Patienter i avancerade njursviktsstadier eller med ökad symtombörda hade en mer negativ sjukdomsuppfattning än de i tidigare stadier.
- Sjukdomsuppfattning korrelerade till HRQoL. En mer negativ sjukdomsuppfattning korrelerade till försämrad HRQoL och även till användning av fr.a. undvikande, fatalistisk, känslomässig och stödjande coping-strategier
- Det fanns en utbredd osäkerhet om upplevda symptom hade med njursjukdomen att göra, vilket antyder en kunskapsbrist hos patienterna, fr.a. i tidigare njursviktsstadier.
- Patienternas HRQoL var nedsatt redan i tidigare stadier och sjönk alltmer med försämrade njurfunktion, fr.a. beträffande fysisk hälsa. Vid tiden för start av kontinuerlig dialysbehandling sågs betydande försämring även beträffande mental hälsa.
- Försämrad HRQoL var korrelerade med inflammation, förekomst av hjärtsjukdom, diabetes, försämrat GFR, högre ålder, övervikt och lägre Hb- och p-albuminvärden
- Inflammation och hjärtsjukdom var framträdande faktorer som ökade risken för sämre HRQoL. Uppmärksamhet på detta är viktigt för njursjukvårdens arbete med sekundärprevention.

## KLINISKA IMPLIKATIONER

En ökad förståelse för individens sjukdomsuppfattning och HRQoL är viktigt för njursjukvården, eftersom dessa hänger ihop med varandra och har betydelse för patientens coping och egenvård. Hänsyn till patientens sjukdomsuppfattning och HRQoL skulle kunna förbättra kommunikationen patient - vårdgivare, och därmed bidra till att förflytta patienten till bättre sjukdomsförståelse, coping och följsamhet samt stödja livsstilsförändringar och egenvård, inklusive att kunna välja självdialys som ett behandlingsalternativ. Vidare kan ett ökat fokus på sjukdomsuppfattning och HRQoL bidra till ökat stöd avseende individens hälsofrämjande ansträngningar, samtidigt som det kan möjliggöra identifiering av risk för otillräcklig egenvård och/eller försämrad HRQoL. Ökat fokus på sjukdomsuppfattning och HRQoL skulle även kunna vara behjälpligt för kliniskt verksam personal att identifiera och fokusera på såväl, för individen, relevanta problem likväl som hälsoresurser.

Resultaten antyder att njursjukvården skulle kunna dra nytta av ett ökat helhetsgrepp, med ökad uppmärksamhet på hälsofrämjande åtgärder beträffande komorbiditet och riskfaktorer. Detta kan exempelvis innefatta åtgärder och uppföljning beträffande blodtryck, blodsocker, matvanor, munhälsa, vikt och nutritionsstatus, sår och infektioner samt livsstilsaspekter som stress, rökning och fysisk inaktivitet.

Kunskaper och strategier för att förbättra sjukdomsuppfattning, HRQoL, coping och egenvård hos njursjuka behövs. Exempel på detta skulle kunna vara patientutbildningsprogram i tidiga njursviktsskeden, systematisk satsning på ökad fysisk aktivitet och utveckling av passande psykosocialt stöd till patienter som är på väg in i dialysbehandling.

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