Chapter 1

Introduction
End-stage renal disease (ESRD) is a life-threatening condition with wide-ranging implications for patients’ lives. Among the available treatments, kidney transplantation is regarded as the best option in terms of patient survival and cost-effectiveness. More recently, evidence has accumulated which suggests that recipients of kidney transplants also experience better health-related quality of life. However, despite advances in our knowledge about the impact of different treatment options for ESRD on patients’ health-related quality of life, the process of adjustment to kidney transplantation remains poorly understood. Some of the issues requiring further investigation are the underlying mechanisms of improvement, explanations for individual differences in outcomes, and long-term impact of kidney transplantation. Accordingly, this research was undertaken to fill a few of these gaps and identify determinants of adjustment to kidney transplantation, with particular focus on individual characteristics of patients. Findings are expected to increase our understanding of the adjustment process after kidney transplantation, and in doing so will hopefully open new avenues to further improve the health-related quality of life of patients living with a kidney transplant.

This opening chapter begins with an introduction to end-stage renal disease and its epidemiology, followed by a brief description of available treatment options. Next, the patient experience and the role individual characteristics may play in the adjustment process is discussed. Subsequently, setting, design, and aims of the two studies conducted for this research project are outlined. The chapter concludes with a brief preview of the individual scientific articles at the heart of this thesis.

**End Stage Renal Disease**

**Definition**

The kidneys fulfil a range of vital functions, including excretion of metabolic waste products, regulation of water and electrolyte metabolism, maintenance of acid-base homeostasis and endocrine functions, such as haemoglobin synthesis, vitamin D metabolism, and modulation of blood pressure. (Rinschen, Völker, & Brinkkötter, 2014). In advanced stages of chronic kidney disease (CKD), most of these functions are disrupted. CKD is defined as “abnormalities of kidney structure or function, present for > 3 months, with implications for health” (Stevens, Levin, & Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members, 2013). According to clinical practice
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guidelines, six stages of CKD are differentiated based on glomerular filtration rate [GFR: a measure of kidney function based on serum creatinine concentration adjusted for age, gender, and ethnicity] and albuminuria [presence of protein in the urine] (Stevens et al., 2013). Stages range from an asymptomatic condition [GFR > 60 mL/min/1.73 m² and urinary albumin < 30 mg/g] to kidney failure [GFR < 15 mL/min/1.73 m² and urinary albumin > 300 mg/g] (Parrish, 2016). The terms kidney failure and ESRD are often used interchangeably, but technically the term ESRD is reserved for situations where renal replacement therapy (RRT) has been initiated (National Kidney Foundation, 2002). However, given that kidney failure is ultimately fatal without adequate treatment in the form of RRT, in the developed world ESRD and kidney failure usually coincide.

Epidemiology
Every year approximately 441,000 people globally initiate RRT, corresponding to an incidence of 73 per million population [pmp] (Anand, Bitton, & Gaziano, 2013). In 2010, 2.6 million people worldwide received RRT, a prevalence of 379 pmp (Liyanage et al., 2015). Forecasts predict that the number of people treated with RRT will more than double by 2030, mainly due to ageing populations and the growing prevalence of diabetes and hypertension (Liyanage et al., 2015).

With a 14 % increase between 2001 and 2014, the incidence of ESRD in the Netherlands is considered relatively stable (United States Renal Data System, 2016). In 2015, 1996 patients (118 pmp) started RRT (Nefrodata, 2016a). However, the prevalence of ESRD in the Netherlands has increased significantly, as indicated by a 49 % rise between 2000 and 2013 (United States Renal Data System, 2016). In 2016 16,727 patients (985 pmp) were registered as treated with RRT (Nefrodata, 2016a).

It is foreseeable that the growing number of patients with ESRD will place enormous demands on health-care budgets. Dialysis and kidney transplantation are amongst the most expensive treatments covered by basic health insurance in the Netherlands. The annual expense for dialysis amounts to approximately € 80,000 to € 120,000 per patient. Kidney transplantation and care for the recipient cost about € 80,000 per patient during the first year, but is considerably less expensive than dialysis in subsequent years (Nierstichting, 2016). In 2011, ESRD ranked 17th among the most expensive conditions in terms of health expenditure in the Netherlands with a total of € 800,000,000 spent on its treatment
These numbers imply that 0.9% of the entire Dutch health care budget was allocated for the treatment of 0.09% of the population. Given the growing prevalence of ESRD and the immense costs associated with its treatment, progress in the prevention and management of ESRD becomes increasingly important.

Treatment

Dialysis

Kidney transplantation aside, dialysis is the only renal replacement therapy for ESRD. Dialysis removes metabolic waste products and corrects imbalances of salt, water, and acid-base homeostasis to some extent [5 – 15% of kidney function (Nierstichting, 2016)], but is unable to substitute endocrine functions of the kidney (Levy, Brown, & Daley, 2009a). Two types of dialysis are distinguished: peritoneal dialysis (PD) and haemodialysis (HD).

In PD the blood is purified inside the body using the peritoneum as a semi-permeable membrane. Dialysate (i.e. cleansing fluid) is introduced into the peritoneal cavity through a catheter and draws excess fluid and metabolic waste products out of the blood. By means of diffusion, the dialysate becomes progressively saturated after which it is drained from the body and replaced, a process referred to as an exchange (Findlay & Isles, 2015; National Kidney Foundation, 2015a; Nierstichting, n.d.). There are two subtypes of PD, continuous ambulatory PD (CAPD) and automated PD (APD). In CAPD, patients themselves carry out four to five exchanges daily during waking hours, each exchange taking 20 –30 minutes. In APD, exchanges are managed automatically by a machine called cycler, with each cycle taking 1 to 1.5 hours. APD usually takes place at home during the night while the patient sleeps (Findlay & Isles, 2015; National Kidney Foundation, n.d.).

In HD, the blood is processed inside an external artificial kidney, also called dialyzer, as part of a dialysis circuit (Levy, Brown, & Daley, 2009a; National Kidney Foundation, 2015b). By means of a vascular access patients’ circulation is connected to the dialyzer, through which blood is pumped and purified in the process. Inside the dialyzer a thin semi-permeable membrane separates the blood from the dialysate, which draws excess fluid and metabolic waste products out of the blood (Levy, Brown, & Daley, 2009a; National Kidney Foundation, 2015b). HD treatment is carried out at hospitals, dialysis centres, or at home. In its most common form, in-centre HD, treatment takes place at a dialysis unit or hospital every other day three times a week with each session taking about four hours (National
Kidney Foundation, 2015a). Some dialysis centres also offer the possibility of night-time HD. Another option is HD at home allowing more frequent dialysis treatment, six or seven times per week with fewer hours per session or with longer sessions during the night (Levy, Brown, & Daley, 2009a; National Kidney Foundation, 2015b).

In 2016, 6,452 patients in the Netherlands were treated with dialysis; 5592 (87 %) with haemodialysis and 860 with peritoneal dialysis, a 34 % increase from 2001 (Nefrodata, 2016a). Dialysis treatment is associated with high mortality. In 2014, 1154 (18 %) of 6466 patients on dialysis in the Netherlands died (ERA-EDTA Registry, 2016).

Kidney transplantation
Kidney transplantation is the preferred treatment option for ESRD because it is associated with lower mortality, more cost-effective, and affords patients better health-related quality of life than dialysis (Klarenbach, Tonelli, Chui, & Manns, 2014; Kontodimopoulos & Niakas, 2008; Liem, Bosch, Arends, Heijenbrok-Kal, & Hunink, 2007; Wyld, Morton, Hayen, Howard, & Webster, 2012). To receive a transplant, patients have to be placed on the waiting list for kidneys from deceased donors, which is only accessible for patients who have started dialysis, or find a living donor willing to donate one of their kidneys. In either case, patients are initially assessed by a consulting nephrologist to ensure their suitability for transplantation. Kidneys of deceased donors are allocated according to a complex system, taking multiple variables, such as histocompatibility, waiting time, urgency, and age into account. Organs from deceased donors are scarce, a fact that is reflected in the average waiting time of over three years observed in the Netherlands (Nederlandse Transplantatie Stichting, 2015). As a consequence, the number of transplantations with living donor kidneys has rapidly increased during the last decade.

The transplant surgery itself takes two to four hours and the native kidneys are only removed if they cause severe problems such as frequent kidney infections (Levy, Brown, & Daley, 2009b; University of California San Francisco, 2016). During surgery the kidney is placed in the anterior part of the lower abdomen in the pelvis in the iliac fossa (Gunabushanam, Matas, & Humar, 2015). After artery and vein of the kidney are joined to iliac artery and vein blood flow to the kidney is restored. The ureter is then joined to the bladder to complete the operation (Gunabushanam et al., 2015; Kidney Research UK, 2013). Recovery in the hospital takes usually three to seven days. After the operation, patient and
kidney are monitored carefully and depending on the success of the procedure and subsequent performance of the transplanted organ, kidney function is partially restored.

Since 2001, there are more patients in the Netherlands who live with a kidney transplant than patients on dialysis (Nefrodata, 2016b). Moreover, the number of patients living with a functioning kidney graft has more than doubled from 4918 in 2001 to 10,275 in 2016 (Nefrodata, 2016b). Since 2008 the majority of transplantations in the Netherlands are performed with kidneys from living donors (Nefrodata, 2016c); of 983 kidney transplantations in 2015, 513 (52 %) involved a living donor kidney (Nederlandse Transplantatie Stichting, 2015). On average, kidneys from living donors survive longer. According to figures for the cohort 2005 - 2009, 94.2 % of kidneys from living donors are still functioning after five years compared to 87.9 % of kidneys from deceased donors (ERA-EDTA Registry, 2016).

**The patient experience**

*Perceived health and psychological distress*

ESRD and dialysis treatment put considerable strain on patients. Besides the time-consuming dialysis sessions, patients treated with dialysis are also required to adhere to restrictions of diet and fluid intake, as dialysis only partially substitutes the functions of the kidney. In addition, patients face distressing symptoms such as fatigue and itching (Danquah, Meininger, Zimmerman, Bergstrom, & Diamond, 2010; Murtagh, Addington-Hall, & Higginson, 2007; Scherer, Combs, & Brennan, 2017). Overall, this implies major disruptions of patients’ lives and contributes to the intrusiveness of the illness and its treatment (Griva, Jayasena, Davenport, Harrison, & Newman, 2009; Polaschek, 2003; Urquhart-Secord et al., 2016). Accordingly, a number of studies have suggested that perceived health is lower and psychological distress higher among patients treated with dialysis than among kidney transplant recipients and the general population (Alvares, Cesar, Acurcio, Gurgel Andrade, & Cherchiglia, 2012; Czyzewski, Sanko-Resmer, Wyzgal, & Kurowski, 2014; Landreneau, Lee, & Landreneau, 2010; Liem et al., 2007; Ozcan et al., 2015; Tonelli et al., 2011).

Kidney transplantation liberates patients from the restrictions imposed by dialysis. However, despite the advantages kidney transplantation has over dialysis treatment in terms of mortality, perceived health and possibly psychological distress, it is not without
drawbacks. While the longevity of kidney transplants has significantly improved, the threat of rejection remains. Besides being a perpetual concern for some patients, this also means that kidney transplantation is in many cases only a temporary solution and a number of patients will outlive their kidney and require a second or even third transplant. Another drawback is that, although individual outcomes might differ substantially, kidney function is rarely restored to the level of healthy individuals. This implies that in many cases some symptoms associated with advanced stages of chronic kidney disease, such as fatigue, will persist, albeit to a lesser degree (Goedendorp, Hoitsma, Bloot, Bleijenberg, & Knoop, 2013). In addition, patients have to take immunosuppressive medication to counter the immune response; genetically unfamiliar tissue is normally attacked by the immune system of the host and causes the kidney to cease functioning (i.e. rejection). While much progress has been made over the last decades, immunosuppressive medication continues to have unpleasant and sometimes severe adverse effects, suspected to accumulate over time (Afshar, Rebollo-Mesa, Murphy, Murtagh, & Mamode, 2012; Kugler et al., 2009; Teng et al., 2015). Furthermore, prolonged exposure to immunosuppressants has been linked to the development of chronic conditions such as cardiovascular diseases, diabetes, and malignancies (AlBugami & Kiberd, 2014; McCaughan & Courtney, 2015; Sharif & Cohney, 2016; Stoumpos, Jardine, & Mark, 2015). These drawbacks of kidney transplantation might explain why perceived health has often been found to remain lower when compared to the general population (Dew et al., 1997; Dobbels, De Bleser, De Geest, & Fine, 2007; Landreneau et al., 2010; von der Lippe et al., 2014; Wei et al., 2013).

Despite the growing number of kidney transplant recipients living for many years with a transplanted kidney, the long-term perspective on patient-reported outcomes has received little research attention. One of the few studies conducted among long-term kidney transplant recipients corroborated that their general health perceptions were lower than those of the general population (Neipp et al., 2006). Whether differences exist in perceived health between short-term and long-term kidney transplant recipients remains presently unknown and is therefore, one of the subjects addressed in this thesis.

According to earlier research, the course of important patient-reported outcomes such as health-related quality of life displays similarities across different types of organ transplants and it has been suggested that sub-groups with a different course can be identified (Goetzmann et al., 2008; Villeneuve et al., 2016). So far, however, no attempts
have been made to discern sub-groups of patients who differ with regards to the course of perceived health and to identify correlates thereof. Results could facilitate early recognition of at-risk patients and thus will be amongst the topics investigated in this thesis.

*Individual characteristics*

Although research has repeatedly found that kidney transplant recipients experience better perceived health and less psychological distress, outcomes vary considerably between patients. Attempts to explain these differences have so far mainly focused on socio-demographic and medical determinants. Most notably, a greater burden in terms of symptoms and comorbidities has repeatedly been linked to reduced perceived health and increased psychological distress (Bohlke et al., 2009; Gentile et al., 2013; Prihodova et al., 2010; Rosenberger et al., 2006). However, given that perceived health and psychological distress are inherently subjective, individual characteristics of patients are likely to have added importance when explaining differences in post-transplant outcomes. Preliminary support for this claim comes from a few studies linking individual characteristics, such as control beliefs and neuroticism to better physical and mental quality of life of kidney transplant recipients (Goetzmann et al., 2008; Griva et al., 2009; Prihodova et al., 2010). Yet, previous research in other patient populations has suggested some additional factors that might play a crucial role in the adjustment process.

Cognitive adaptation theory (Taylor, Kemeny, Reed, Bower, & Gruenewald, 2000; Taylor, 1983) proposes that aside from perceived control, optimism and self-esteem are of particular significance. Firstly, perceived control refers to an individual’s belief that important outcomes in one’s life are under one’s control. Higher levels of perceived control were shown to be associated with better perceived health and less psychological distress in the general population, as well as across a range of illnesses, including ESRD (Birmele, Le Gall, Sautenet, Aguerre, & Camus, 2012; Gadalla, 2009; Griva et al., 2009; Helgeson, Reynolds, Siminerio, Becker, & Escobar, 2014; Stewart & Yuen, 2011; Theofilou, 2012). Secondly, optimism, defined as a generalized expectation of positive outcomes (Scheier & Carver, 1985), is reported to have beneficial effects on adjustment and psychological distress in different patient populations (Avvenuti, Baiardini, & Giardini, 2016; Nes & Segerstrom, 2006; Rasmussen, Scheier, & Greenhouse, 2009; Stewart & Yuen, 2011). Finally, self-esteem refers to global feelings of self-worth (Rosenberg, 1965) and the process of
regaining self-esteem is hypothesized to be another fundamental task in the adjustment process (Taylor, 1983). Accordingly, a number of studies suggest that self-esteem makes a positive contribution to adjustment (Christianson, Weis, & Fouad, 2013; Peter, Mueller, Cieza, & Geyh, 2012; Stewart & Yuen, 2011). In this thesis, these three characteristics will be examined as potential mediators in the relationship between objective health and psychological distress.

An additional variable to be examined is the expectations of patients. Previous research indicates that patients overestimate the quality of life they will achieve after transplantation (Cleemput, Kesteloot, De Geest, Dobbels, & Vanrenterghem, 2003; Smith et al., 2008; Trivedi, Rosaasen, & Mansell, 2016). Yet, it remains unknown whether this overestimation might result in increased psychological distress. This thesis aims to answer this question and clarify the role of optimism in this process.

While previous research suggests that levels of perceived control are higher among kidney transplant recipients than among dialysis patients (Griva et al., 2009; Griva, Davenport, Harrison, & Newman, 2012) it is unclear whether these differences reflect actual changes of perceived control instigated by transplantation. In addition to addressing this subject this thesis will investigate whether potential changes in perceived control affect the course of psychological distress.

A number of studies suggest that psychological functioning improves after kidney transplantation (Landreneau et al., 2010; Liem et al., 2007; Ozcan et al., 2015), yet the underlying process remains unclear. Self-regulation theory might offer a useful framework to understand this phenomenon. According to this perspective, individuals have an inherent tendency to pursue personal goals (Heckhausen, Wrosch, & Schulz, 2010). Moreover, research indicates that medical conditions can impede important goals, with negative consequences for well-being (Janse, Sprangers, Ranchor, & Fleer, 2016; Stefanic, Caputi, & Iverson, 2014). Kidney transplantation is likely to remove many impediments and could in this way improve well-being. Therefore, this thesis will examine changes in goal disturbance after kidney transplantation and their relationship with changes in psychological distress and explore whether this association is mediated by perceived control.
CHAPTER 1

Outline of research

Setting and design

The current research project included two independent studies conducted among patients of the University Medical Center Groningen (UMCG). Located in the North, the UMCG is one of the largest hospitals in the Netherlands with more than 10,000 employees and room for more than 1300 patients, providing medical care for more than three million people living in the provinces Groningen, Friesland, and Drenthe and beyond. The UMCG is also the largest transplant centre in the Netherlands and since 2007 among the few hospitals in the world to perform all forms of organ [kidney, heart, lung, liver, pancreas, and small intestine] and tissue transplants in adults and children. Transplantation has been a cornerstone of the UMCG ever since the first kidney transplant in Groningen was performed in 1968 (University Medical Center Groningen, 2009). In 2015, a total of 176 kidney transplantations were performed in the UMCG, not including combined transplantations of more than one organ (Nederlandse Transplantatie Stichting, 2015).

The first study employed a cross-sectional design and was conducted among patients who had received a kidney transplant at the UMCG between 1993 and 2008 and were still living with a functioning kidney graft at the time of data collection. The second study used a prospective design and followed patients between 2008 and 2013 from the waiting list for kidney transplantation in the UMCG until one year after transplantation. At the time this study was initiated, patients on the waiting list in the UMCG emanated from dialysis centres located in Almelo, Apeldoorn, Deventer, Emmen, Enschede, Groningen, Leeuwarden and Zwolle. Patients were assessed once a year until they were transplanted. After successful transplantation, patients were assessed again at three, six and twelve months post-transplant. At each assessment, data were collected on socio-demographic variables, symptoms, comorbidity, perceived health, psychological distress, perceived control, optimism, self-esteem, and quality of life.

Aims

The main objective of the studies included in this thesis was to clarify how individual characteristics might influence perceived health and psychological distress. Chapter 2 deals with the evaluation of the long-term impact of kidney transplantation on perceived health and identifies differences between short- and long-term kidney transplant recipients.
Chapter 3 investigates the interrelation of objective health and psychological distress and how it is affected by perceived control, optimism, and self-esteem. Chapter 4 examines how patients’ quality of life expectations prior to transplantation affect post-transplant psychological distress and clarifies the role of optimism in this process. Chapter 5 describes three patterns of change in perceived control from pre- to post-transplant and explores whether these patterns are differentially related to the course of psychological distress. Chapter 6 explores the association of pre- to post-transplant changes in goal disturbance and importance with changes in psychological distress and whether this association is mediated by perceived control. Chapter 7 identifies trajectories of perceived health and predictors thereof, among kidney and liver transplant recipients, in an attempt to develop a model for early recognition of patients at risk of poor post-transplant outcomes. Finally, Chapter 8 discusses the conclusions drawn from previous chapters and the potential implications of findings for future research and clinical practice.

It is anticipated that the improved understanding of the role of individual characteristics for the adjustment process of kidney transplant recipients could help to facilitate the identification of patients at-risk of suboptimal outcomes after kidney transplantation. Conversely, results of this thesis could highlight key components for interventions aiming to improve patients’ perceived health and psychological distress. Expectations are that this might eventually contribute to a further increase in the number of patients able to enjoy the maximum benefits life after kidney transplantation can potentially offer.
REFERENCES


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