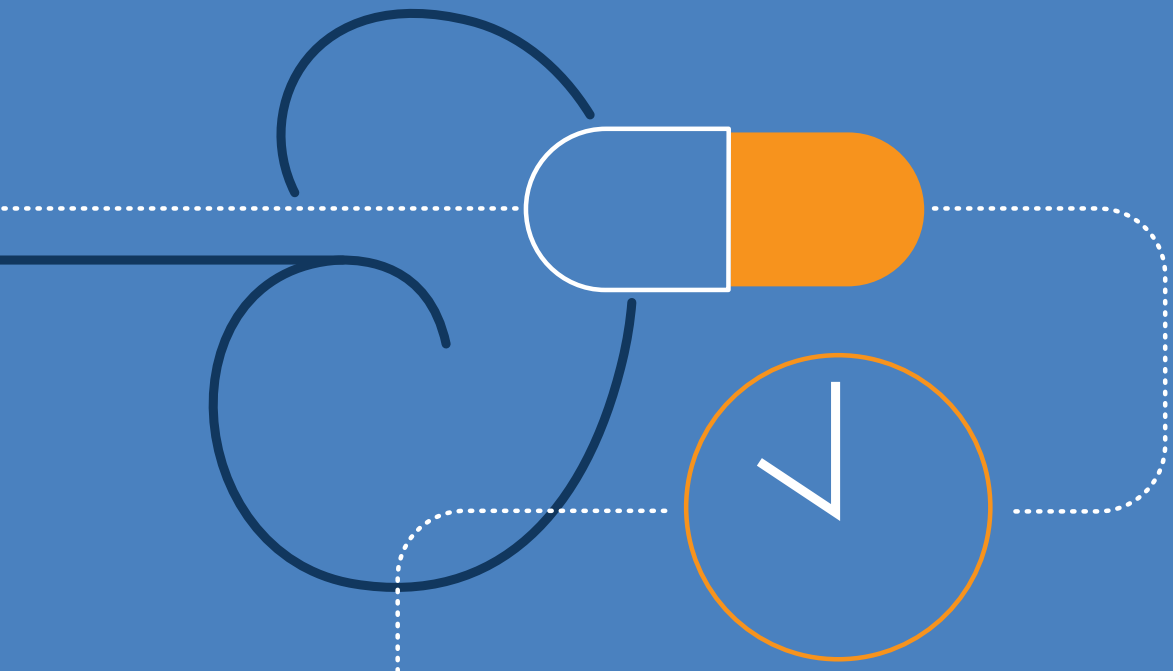


PSYCHOSOCIAL ASPECTS OF MEDICATION NONADHERENCE AFTER KIDNEY TRANSPLANTATION

MIRJAM TIELEN

PSYCHOSOCIAL ASPECTS OF MEDICATION NONADHERENCE AFTER KIDNEY TRANSPLANTATION

Onderzoek naar de psychosociale aspecten van medicatie therapieontrouw na niertransplantatie

Mirjam Tielen

ISBN: 978-94-6233-227-0
Cover design: Thijs van Traa, Webwonders
Layout and printed by Gildeprint, Enschede

The research presented in this thesis was performed at the Departments of Nephrology & Transplantation of the Erasmus University Medical Center of Rotterdam. The research was supported by an internal Erasmus MC grant 'Evidence Based Care by Nurses'.

Financial support by the Erasmus University Medical Centre of Rotterdam, The Dutch Kidney Foundation, Astellas Pharma B.V., Shire International B.V. and Dutch Transplant Society for the publication of this thesis is gratefully acknowledged.

PSYCHOSOCIAL ASPECTS OF MEDICATION NONADHERENCE AFTER KIDNEY TRANSPLANTATION

Onderzoek naar de psychosociale aspecten van medicatie therapieontrouw na niertransplantatie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

Woensdag 06 april 2016 om 11:30 uur

Mirjam Tielen
geboren te Eindhoven

Erasmus University Rotterdam

Promotiecommissie

Promotor
Prof.dr. W. Weimar

Overige leden
Prof.dr. J.J. van Busschbach
Prof.dr. T. van Gelder
Prof.dr. S. de Geest

Copromotor
Dr. E.K. Massey

Contents

1

Introduction

"Sometimes I am scared because I think that if I lose this kidney, I'll regret that I didn't take my medication"
(Kidney transplant patient)

"*When you miss a dose you presume it is ok and you move on and nothing happens. And so on, until I went to the outpatient clinic to check my kidney function and it wasn't ok anymore*"
(Kidney transplant patient after graft loss)

In my work as a nurse practitioner, I see a lot of patients who have difficulties with taking immunosuppressive medication after kidney transplantation. They struggle to fit the medication into their daily life. This phenomenon intrigued me, why do patients act in a certain way that can lead to rejection of their graft. How do patients think about their medication and how does this affect their behavior?

End stage renal disease

Patients with end stage renal disease (ESRD) have various options for renal replacement therapy. Patients can undergo dialysis or kidney transplantation. While dialysis is a lifesaving treatment, transplantation, if possible, is the best option due to the advantages for patient survival and quality of life (www.renine.nl) (1). There are two choices in renal transplantation; a living donor kidney transplantation (LDKT) or a deceased donor kidney transplantation (DDKT). A LDKT is the most favourable, because of the advantages for graft and patient survival (2-4). Moreover it can be performed before dialysis has to be instituted. Thus dialysis related morbidity and mortality can be circumvented. With a kidney transplant a patient can live a relatively normal life without the limitations of dialysis, however the patient must take lifelong immunosuppressive medication to prevent rejection of the graft. Because of this medication regime they receive specific lifestyle recommendations.

Therapy and lifestyle after kidney transplantation

Kidney transplant patients have to take immunosuppressive drugs every twelve-hours. A recent development is monotherapy once a day (5, 6). Most patients have a medical regime of two intake moments a day. In many cases patients have to take other medications in addition to their immunosuppressive drugs. Immediately after kidney transplantation when patients have to take medication, this consists of on average of at least 6 pills in the morning depending on the co-morbidity of the patient. Each medication can have specific conditions under which it can be taken, such as not in combination with other drugs or after food, the entire regime as a whole can be complex. The complexity of the regime is suggested to influence adherence (7-9). Because of the immunosuppressive medication patients are

more vulnerable for infections, and therefore have recommendations for diet to prevent a bacterial infection. Their diet is similar to the diet of pregnant women. Rates of skin cancer after kidney transplantation are high, the immunosuppressive medication makes the skin more vulnerable. Almost 40% of the post-transplant malignancies are skin cancer (10). Patients are therefore advised to avoid direct sun exposure. Also immunosuppressive medications have many side effects, including diabetes, cosmetic side effects, diarrhea, and tremors (11). This can have an effect on patient's quality of life after transplantation. Because patients can experience side effects while benefits of the medication are not always evident this can influence their adherence. This can be likened to blood pressure medication whereby patients do not feel/experience benefits but do experience side effects (12, 13). These could be factors, which may affect medication adherence after kidney transplantation.

Medication Adherence

According to the World Health Organization (WHO) adherence is defined as "the extent to which a person's behavior corresponds with the agreed recommendations from a health care provider" (7). Nonadherence to the medication regime in chronically ill patients is related to poorer clinical outcomes (7, 14). After kidney transplantation we now see evidence that nonadherence has a negative influence on graft survival in the long term (15-17). Nonadherence is also associated with increased healthcare costs (18, 19).

One of the difficulties with adherence research is the issue of measurement. The gold-standard to measure nonadherence is direct observation that medication was consumed (20). However this is not a realistic tool, you cannot always be there to observe your patient, especially after discharge from hospital. As each type of measurement has limitations, combining several measures of adherences, so called 'triangulation', is recommended (21).

According to the WHO there are five interacting dimensions that affect adherence. The first is 'social and economic factors', for example poverty, race and age, insurance of the patient. The second dimension is 'the health care team and system-related factors', such as patient-provider relationship. The third dimension 'condition-related factors' is the severity of symptoms or severity of the disease and how they influence patients' perception of risk if they deviate from the prescribed regime. The fourth dimension is 'therapy-related factors' like the complexity of the medical regime and the side effects of that regime. The fifth and last dimension is 'patient-related factors' which represents the resources, knowledge, attitudes, beliefs, perceptions, and expectations of the patient.

Most studies on non-adherence focus on 'therapy-related factors' (22, 23). Less is known about the second dimension 'the health care team and system-related factors' or the fifth dimension 'patient-related factors'. Examples of patient-related factors are the attitudes and beliefs of the patients. In other patient groups, evidence suggests that these patient-related, psychosocial factors influence adherence (24, 25). Moreover, most of the research

on nonadherence is cross-sectional (15); consequently there is a great variation in time since kidney transplantation. Adherence and factors that cause it may be different at different phases after transplantation. There is thus a need for prospective studies to investigate the rate of nonadherence immediately after transplantation and changes over time as well as potential determinants of nonadherence.

A meta-analysis showed that in kidney transplantation there is a nonadherence rate of 35.6 cases per 100 persons per year (15). Nonadherence is more common among adolescents compared to other age groups (26, 27). Many studies focus mainly on the adolescent in paediatric care (aged 12-18 years) and the effect of transition from paediatric to adult care on adherence (28-30). However, less is known about nonadherence rates of the young adult in adult care (>18 years) and who of the young adults are at risk. To our knowledge, there is also hardly any evidence about elderly (>65 years) and their non-adherence rate in kidney transplantation. Research among elderly and nonadherence in antihypertensive medication showed that half of patients forget their medication (31). Patients that are classified as nonadherent can have problems with the taking, dosing, and timing of the prescribed medicines (32). The complexity of the regime is suggested to have influence on adherence (7-9). When patients get older (>65 years) this can even be more difficult due to their aging process.

Graft survival in kidney transplantation

After transplantation the survival of the graft depends on different factors. Patients who are transplanted with a LDKT have significant patient and graft survival benefits when compared with DDKT (2). In DDKT there is damage due to type and length of cold storage and therefore the quality of the kidney (33). In contrast, living donor nephrectomy is planned in an optimized setting. Moreover, the donor is screened and therefore is in an excellent state of health. Patients who are transplanted pre-emptively (prior to initiation of dialysis) with a living donor kidney have the best clinical outcomes (34, 35). Also the least mismatches on the human leukocyte antigen (HLA)-A, -B, -DR contributes to a better graft survival (3, 35). Since the 1990's more effective immunosuppressive drugs with fewer side effects are available to prevent rejection. Nevertheless rejection can occur after transplantation and can influence graft survival. Patients with a previous transplant or sensitized patients with a high level of a panel-reactive antibodies can develop an early and aggressive form of rejection, termed AMR (36). For this type of rejection there is no standard treatment. The most common form of immunological rejection in the early post-transplant period is acute cellular rejection; the impact of acute cellular rejection on graft survival depends on the response to treatment (37). Younger patients have a more vigorous immune system, resulting in more rejection (23, 38). The immunosuppressive drugs, especially calcineurin inhibitors, can cause nephrotoxicity. The avoidance of clinical or subclinical episodes of

nephrotoxicity may be important in terms of long-term allograft histology and function (39). Recurrence of original disease, infections with bacteria or virus, can also play a role in the graft survival. The short term survival has increased over recent years, 1-year graft survival rates are typically above 90%, while the long-term graft survival rates have remained unchanged at 4% graft loss per year (40, 41). Risk factors for chronic allograft loss are donor organ quality, immune factors, but also recipient factors like hypertension, proteinuria, smoking and medication non-adherence (42). Late acute rejection is often seen in the clinic and it may be the result of medication non-adherence. The rejection is often severe and is associated with de novo donor specific antigen (DSA) and vascular rejection that can result in graft loss. However there is little evidence of prospective studies investigating if medication nonadherence (in timing) has influence on rejection rate or graft survival. More important we still do not know the characteristics, behavior and beliefs of patients at risk for nonadherence and therefore for graft loss.

Aim and outline of this Thesis

The overarching aim was to gain a better understanding of medication nonadherence and in particular the psychosocial aspects of behavior after kidney transplantation in order to inform the care that nurse practitioners can offer in the clinic. To understand how patients cope with their medication regime in daily life, it is important to understand how they perceive their illness and medication as well as how this medication regime fits into, or conflicts with, their daily life. What can we, as healthcare professionals, contribute to the care of our patients so that they become more adherent, how can we achieve the best graft survival in kidney transplant patients with the best quality of life.

Research questions were:

(1) What is the rate of nonadherence among our population of kidney transplant recipients and does this change over time?

(2) What are the attitudes, beliefs and goals of kidney transplant recipients towards the medication regime?

(3) To what extent are these attitudes, beliefs and goals related to nonadherence?

(4) To what extent is nonadherence related to graft survival?

The research questions were answered in the following chapters:

Chapter 2: Describes a mixed-methods Q-methodology study that investigate attitude to nonadherence among young adult renal recipients.

Chapter 3: A descriptive study about attitudes and behavior of young adults towards the medical regime.

Chapter 4: A q-methodological study into the attitudes towards medication non-adherence in elderly kidney transplants patients.

Chapter 5: Describes a prospective cohort study on the role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence up to 6 months after kidney transplantation.

Chapter 6: Describes a prospective cohort study into immunosuppressive medication adherence up to 18 months after kidney transplantation.

Chapter 7: Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study.

Chapter 8: General discussion & Clinical implications

References

1. Hemke AC, Heemskerk MB, van Diepen M, Weimar W, Dekker FW, Hoitsma AJ. Survival prognosis after the start of a renal replacement therapy in the Netherlands: a retrospective cohort study. BMC Nephrol. 2013;14:258.
2. Liem YS, Weimar W. Early living-donor kidney transplantation: a review of the associated survival benefit. Transplantation. 2009 Feb 15;87(3):317-8.
3. Laging M, Kal-van Gestel JA, Haasnoot GW, Claas FH, van de Wetering J, Ijzermans JN, et al. Transplantation results of completely HLA-mismatched living and completely HLA-matched deceased-donor kidneys are comparable. Transplantation. 2014 Feb 15;97(3):330-6.
4. Laging M, Kal-van Gestel JA, van de Wetering J, Ijzermans JN, Weimar W, Roodnat JI. The relative importance of donor age in deceased and living donor kidney transplantation. Transpl Int. 2012 Nov;25(11):1150-7.
5. van Boekel GA, Kerkhofs CH, Hilbrands LB. Treatment satisfaction in renal transplant patients taking tacrolimus once daily. Clin Ther. 2013 Nov;35(11):1821-9 e1.
6. Kuypers DR, Peeters PC, Sennesael JJ, Kianda MN, Vrijens B, Kristanto P, et al. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. Transplantation. 2013 Jan 27;95(2):333-40.
7. WHO. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization2003.
8. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001 Aug;23(8):1296-310.
9. Kamila P, Smith SG, Patzer R, Wolf MS, Marina S. Medication regimen complexity in kidney and liver transplant recipients. Transplantation. 2014 Oct 15;98(7):e73-4.
10. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011 Aug;65(2):263-79; quiz 80.
11. Borda B, Lengyel C, Varkonyi T, Kemeny E, Ottlakan A, Kubik A, et al. Side effects of the calcineurin inhibitor, such as new-onset diabetes after kidney transplantation. Acta Physiol Hung. 2014 Sep;101(3):388-94.
12. Fletcher BR, Hartmann-Boyce J, Hinton L, McManus RJ. The Effect of Self-Monitoring of Blood Pressure on Medication Adherence and Lifestyle Factors: A Systematic Review and Meta-Analysis. Am J Hypertens. 2015 Feb 26.
13. De Geest S, Ruppar T, Berben L, Schonfeld S, Hill MN. Medication non-adherence as a critical factor in the management of presumed resistant hypertension: a narrative review. EuroIntervention. 2014 Jan 22;9(9):1102-9.
14. Dobbels F, Moons P, Abraham I, Larsen CP, Dupont L, De Geest S. Measuring symptom experience of side-effects of immunosuppressive drugs: the Modified Transplant Symptom Occurrence and Distress Scale. Transpl Int. 2008 Aug;21(8):764-73.
15. Butler JA, Peveler RC, Roderick P, Smith PW, Horne R, Mason JC. Modifiable risk factors for non-adherence to immunosuppressants in renal transplant recipients: a cross-sectional study. Nephrol Dial Transplant. 2004 Dec;19(12):3144-9.
16. De Geest S, Sabate E. Adherence to long-term therapies: evidence for action. Eur J Cardiovasc Nurs. 2003 Dec;2(4):323.
17. Dew M, DiMartini A, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, et al. Rates and Risk Factors for Nonadherence to the Medical Regimen After Adult Solid Organ Transplantation. Transplantation. 2007;83(7):858-73.

18. Vlaminck H, Maes B, Evers G, Verbeke G, Lerut E, Van Damme B, et al. Prospective Study on Late Consequences of Subclinical Non-Compliance with Immunosuppressive Therapy in Renal Transplant Patients. Am J Transplant. 2004;4(9):1509-13.
19. Dobbels F, Vanhaecke J, Dupont L, Nevens F, Verleden G, Pirenne J, et al. Pretransplant Predictors of Posttransplant Adherence and Clinical Outcome: An Evidence Base for Pretransplant Psychosocial Screening. Transplantation. 2009;87(10):1497-504.
20. Cleemput I, Kesteloot K, Vanrenterghem Y, Sabina De G. The Economic Implications of Non-Adherence after Renal Transplantation. PharmacoEconomics. 2004;22(18):1217-34.
21. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant Outcomes and Economic Costs Associated with Patient Noncompliance to Immunosuppression. American Journal of Transplantation. 2009;9(11):2597-606.
22. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R, et al. Nonadherence consensus conference summary report. Am J Transplant. 2009 Jan;9(1):35-41.
23. Schäfer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic Accuracy of Measurement Methods to Assess Non-Adherence to Immunosuppressive Drugs in Kidney Transplant Recipients. American Journal of Transplantation. 2008;8(3):616-26.
24. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. Journal of Psychosomatic Research. 1999;47(6):555-67.
25. Horne R, Parham R, Driscoll R, Robinson A. Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. Inflammatory Bowel Diseases. 2009;15(6):837-44.
26. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatric transplantation. 2005;9(3):381.
27. Rianthavorn P, Ettenger RB. Medication non-adherence in the adolescent renal transplant recipient: a clinician's viewpoint. Pediatr Transplant. 2005 Jun;9(3):398-407.
28. Schidlow DV, Fiel SB. Life beyond pediatrics. Transition of chronically ill adolescents from pediatric to adult health care systems. Med Clin North Am. 1990 Sep;74(5):1113-20.
29. Watson AR. Non-compliance and transfer from paediatric to adult transplant unit. Pediatr Nephrol. 2000 Jun;14(6):469-72.
30. Watson AR. Problems and pitfalls of transition from paediatric to adult renal care. Pediatr Nephrol. 2005 Feb;20(2):113-7.
31. Lo SH, Chau JP, Woo J, Thompson DR, Choi KC. Adherence to Antihypertensive Medication in Older Adults With Hypertension. J Cardiovasc Nurs. 2015 Mar 13.
32. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008 May 17;336(7653):1114-7.
33. Hosgood SA, Barlow AD, Yates PJ, Snoeijs MG, van Heurn EL, Nicholson ML. A pilot study assessing the feasibility of a short period of normothermic preservation in an experimental model of non heart beating donor kidneys. J Surg Res. 2011 Nov;171(1):283-90.
34. Cosio FG, Alamir A, Yim S, Pesavento TE, Falkenhain ME, Henry ML, et al. Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. Kidney Int. 1998 Mar;53(3):767-72.
35. Johnson RJ, Fuggle SV, O'Neill J, Start S, Bradley JA, Forsythe JL, et al. Factors influencing outcome after deceased heart beating donor kidney transplantation in the United Kingdom: an evidence base for a new national kidney allocation policy. Transplantation. 2010 Feb 27;89(4):379-86.
36. Racusen LC, Haas M. Antibody-mediated rejection in renal allografts: lessons from pathology. Clin J Am Soc Nephrol. 2006 May;1(3):415-20.

37. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med. 2003 Dec 11;349(24):2326-33.

38. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int. 2001 Oct;60(4):1565-70.

39. Solez K, Vincenti F, Filo RS. Histopathologic findings from 2-year protocol biopsies from a U.S. multicenter kidney transplant trial comparing tarolimus versus cyclosporine: a report of the FK506 Kidney Transplant Study Group. Transplantation. 1998 Dec 27;66(12):1736-40.

40. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant. 2004 Aug;4(8):1289-95.

41. McDonald S, Russ G, Campbell S, Chadban S. Kidney transplant rejection in Australia and New Zealand: relationships between rejection and graft outcome. Am J Transplant. 2007 May;7(5):1201-8.

42. Nankivell BJ, Kuypers DR. Diagnosis and prevention of chronic kidney allograft loss. Lancet. 2011 Oct 15;378(9800):1428-37.

2

Q-Methodology to Identify Young Adult Renal Transplant Recipients at Risk for Nonadherence

Mirjam Tielen[1], AnneLoes van Staa[2,3], Susan Jedeloo[3], N. Job A. van Exel[2] and Willem Weimar[1].

[1] Department of internal medicine, University Medical Center, Erasmus MC, Rotterdam, The Netherlands.
[2] Department of Health Policy and Management (iBMG), Institute for Medical Technology Assessment (iMTA), Erasmus MC, Rotterdam, The Netherlands.
[3] Expert Center Transitions of Care, Rotterdam University, University of Applied Sciences, Rotterdam, The Netherlands.

Transplantation 2008;85: 700-706

Abstract

Background: Young adult renal transplant recipients may display patterns of behavior that affect graft survival. The present study aimed to identify young adults at risk of non-adherent behavior by investigating their attitudes about post-transplant health lifestyle.

Method: A Q-methodological study was conducted. Participants were asked to rank-order statements on issues potentially associated with (non-)adherence, according to agreement. Factor analysis was applied to uncover similar patterns in the ranking of statements. The resulting factors represent attitudes and are described using a composite ranking of the statements. As a first test of discriminated validity, a different group of 34 young patients was asked how well the factor descriptions fitted them.

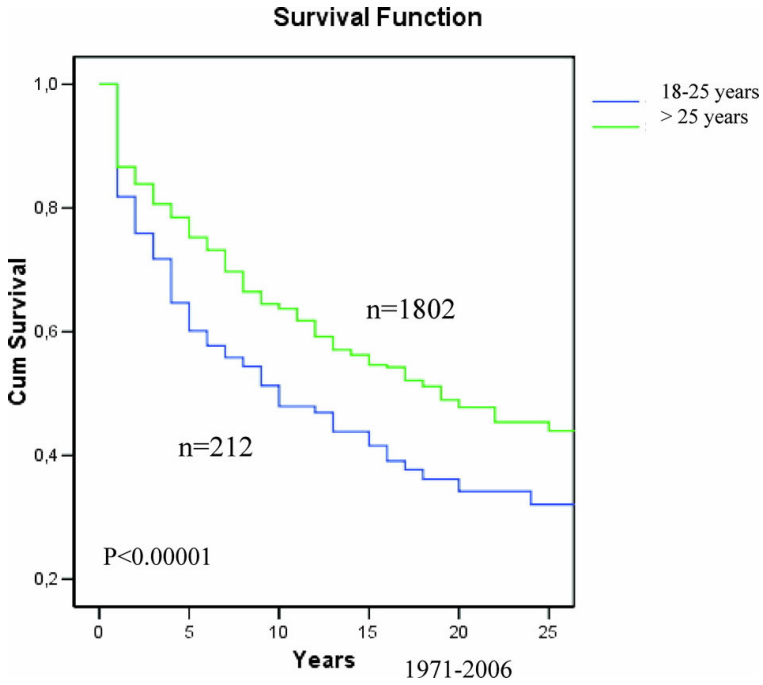
Results: 26 young adults (18-25 years) participated in the study. They were remarkably willing to discuss sensitive issues when confronted with statements on the cards. Four distinct attitude profiles concerning post-transplant health lifestyle were found among young adults: (i) concerned & controlled, (ii) appearance orientated, (iii) opinionated & independent, and (iv) easy going & pliable. Self-categorization discriminated well in 67% of the respondents between the four attitude profiles.

Conclusions: Using Q-methodology, four attitude profiles about post-transplant health lifestyle were uncovered. Self-categorization on these attitudes seems feasible and may be a useful screening aid to identify young adults at risk of non-adherence.

Introduction

Many studies have indicated that renal graft survival is significantly worse in young adults when compared with adults [1,2]. Also in our center we found a lower graft survival in patients of 18 to 25 years of age compared to older recipients (Fig 1) [3].

Figure 1 Graft survival censored for death after kidney transplantation (no exclusions) in Rotterdam stratified for age.



It is generally assumed that young adults have a more vigorous immune system, resulting in more rejection [1,4]. This may, however, not be the only explanation for the difference in graft survival with the adult population. Nonadherence to the post-transplant therapeutic regimen, especially nonadherence to medication, was demonstrated to be a major source of graft loss and morbidity among young adult renal transplant recipients [5-8]. This illustrates, as Dobbels et al. [9] also argued, that young adult transplant recipients should be regarded as a chronically ill patient population in whom behavioral and psychosocial management is equally important as state-of-the-art medical management. Some studies have attempted to categorize transplant recipients according to adherence, mostly using self-reports of medication intake, observational data of blood levels, or medical staff opinion [e.g.,7,10-14]. These studies confirmed the association between non-adherence and adverse effects

for the patient. Other studies have investigated associations between adherence and individual and contextual variables [e.g.,8,11-13,15,16]. These studies found associations between adherence and, among others, gender, satisfaction with appearance, symptoms of posttraumatic stress disorder, self-awareness, denial, and various parental and young adult-parent relationship variables.

These studies provided valuable insights into possible characteristics of young adult transplant recipients at risk of non-adherence and their environment. Many of these authors recommended further investigation into instruments that help identify patients at risk of non-adherence, as necessary aid for the design of effective interventions to increase patient survival and well being [8,11,13,15]. However, such investigations have not been conducted yet. The present study aimed to identify young adults at risk for non-adherent behavior by investigating their attitudes about posttransplant health lifestyle, and to explore the usefulness of the composite profiles in daily practice.

Methodology

To investigate young adults' attitudes about their health lifestyle, a Q-methodological study was conducted. Q-methodology is a hybrid qualitative–quantitative method that provides a foundation for the systematic study of subjectivity, peoples' viewpoints, beliefs, attitudes, feelings, opinions and the like [17-19]. It combines the strengths of qualitative and quantitative research [20], and is regarded a more robust technique than alternative methods for the measurement of attitudes and subjective opinion [21]. Q-methodology was used before to investigate health lifestyle attitudes among youths [22].

In a Q-methodological study, people typically are presented with a sample of statements. Respondents are asked to rank-order these statements according to their point of view, in this case according to agreement, using a quasi-normal distribution (Fig 2).

The individual rankings of statements are factor-analysed so as to reveal a limited number of corresponding patterns in the way the statements were sorted by respondents. Correlation between individual rankings of statements is viewed as an indication of similar viewpoints. Therefore, the results of a Q-methodological study can be used to describe a population of viewpoints, not a population of people [23]. Q-methodology research emphasizes the qualitative 'how' and 'why' people think the way they do; the methodology does not count 'how many' people think a certain way. The goal of Q-methodology is, first and foremost, to uncover different patterns of thought and not their numerical distribution among the larger population [24]. Finally, it is a small sample methodology: "Q does not need large numbers of subjects as does survey analysis, for it can reveal a characteristic independently of the distribution of that characteristic relative to other characteristics" [25].

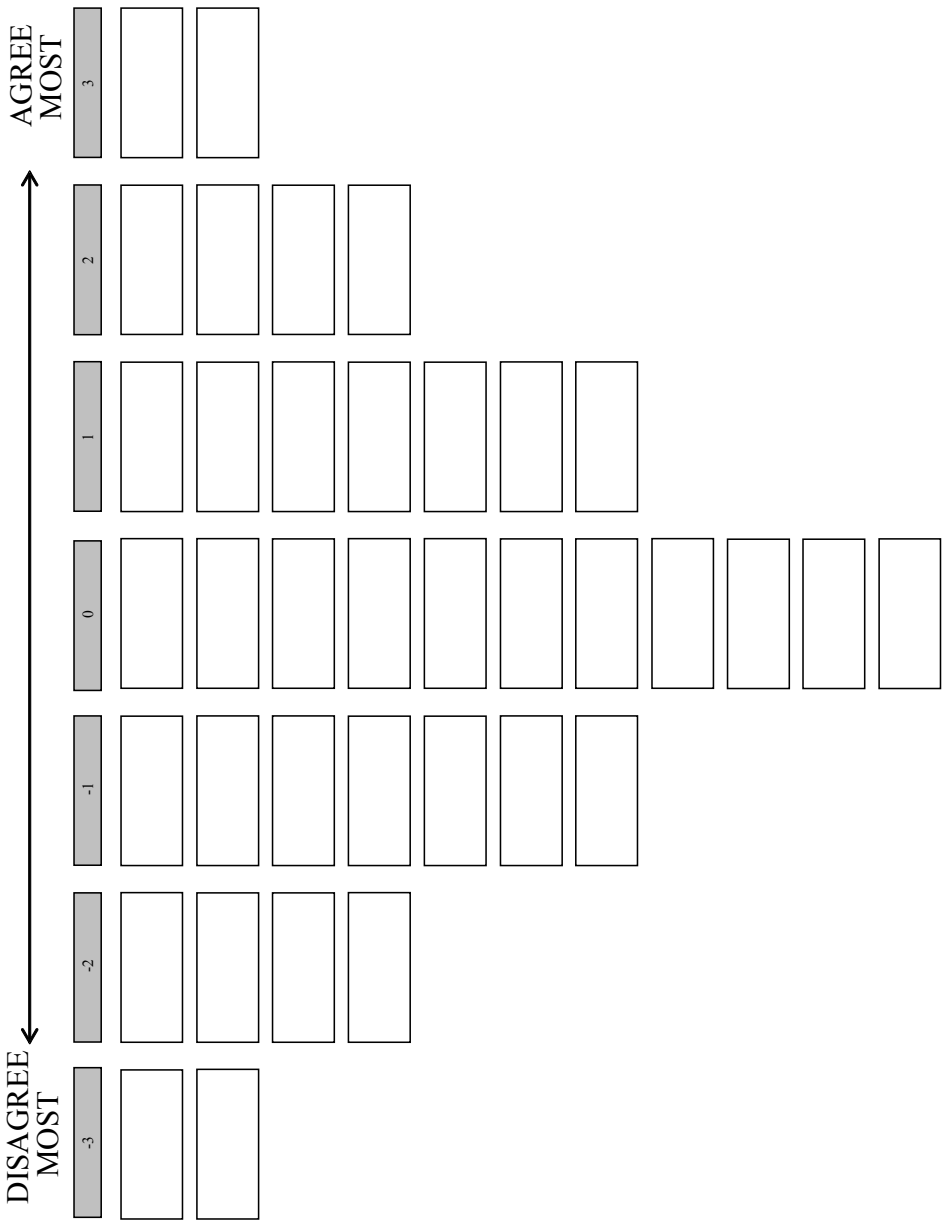


Figure 2 The grid

Table 1 Statements and factor array

Statements	Post-transplant health lifestyle attitudes			
	Profile A (Concerned & controlled)	Profile B (Appearance orientated)	Profile C (Opinionated & independent)	Profile D (Easy going & pliable)
1. I rather not tell others that I have a renal transplant	-1	2**	-1*	-2
2. I am worried that my kidney will reject	3**	1	1	0
3. I can take good care of myself	1	1	1	0
4. Luckily my parents help me think of my medication and appointments	0	0	0	0
5. I want to live my life like my friends do	0	0	1	1
6. I find it hard to bear that my medication makes me thicker	1*	0	-1	-1
7. When I stay in bed late, I just take my medication later	0	1	0	0
8. Healthcare professionals should also discuss sex, relationships and genetics with me	1	1	1	0
9. I don't want to go back on dialysis ever again	0*	-1*	3**	-2*
10. Sometimes I am afraid I will never get into a lasting relationship	-1	1**	-3*	-1
11. My appearance is not very important to me	-1	-3	-1	-2
12. My parents are overprotective and interfere too much in my life	-1	-1	-2**	1*
13. It is annoying that friends sometimes treat me differently only because I have a renal transplant	0	-1	0	0
14. I get tired sooner than my peers	1**	-1	-2*	-1
15. I have no problem swallowing larger pills	0	-1	0	2**
16. I do what the doctors tell me, they know what is best for me	0	0	1	0
17. I find it difficult to draw the line when I am with friends	-2**	0	-1	3**
18. I really never forget my medication	2	2	-1	-1
19. I can do everything I want, even though I have a renal transplant	-1**	3**	1	1
20. I am not concerned about the future	-3**	-1	0	1
21. I don't mind the scars from transplant surgery	0**	-3**	1	1
22. I am more cautious because the kidney was donated by my father or mother	2	-2	2	-1
23. I would appreciate meeting with other young kidney transplant patients	0	0	-2**	1
24. I experience no side-effects from my medication	-2	0	0	-3
25. For most of my medication I don't know why I take it	-1	-2	-3	-1
26. It is more important to enjoy life than to be compliant	-2	0	0	2**
27. When I am out with friends, I am not so very particular with my medication	-3	-1	-1	-2

Statements	Post-transplant health lifestyle attitudes			
	Profile A (Concerned & controlled)	Profile B (Appearance orientated)	Profile C (Opinionated & independent)	Profile D (Easy going & pliable)
28. Healthcare professionals may confront me with the consequences, when I do not comply with the regime	1	0	2	2
29. If you forget your medication once in a while, nothing really bad will happen	-2**	0	-1	3**
30. I often feel gloomy and depressed	0*	-2	-2	-1
31. Thanks to the renal transplant, I can now live a normal life	1	2	2	0*
32. At the outpatient clinic they treat me as an adult	2	1	0	1
33. A pillbox is a handy aid	-1	2	0	2
34. It is important the outpatient clinic monitors my kidney function regularly	3	1	2	0*
35. I don't want my life to evolve around my disease	1**	3	3	-3**
36. If I do something that is not so healthy I tend to feel guilty	2**	-2**	0	0
37. I know what the symptoms of a rejection are and when to call my doctor for help	0	0	0	0

A '-3' score indicates that a typical young adult with that health lifestyle attitude would disagree most with that statement, a '+3' score that (s)he would agree most. Statements with a +3, +2, -2, or -3 score on a factor are called characterizing for that factor. Statements with a statistically different rank-order on a factor when compared with all other factors (marked with * or **) are called distinguishing statements for that factor. Characterizing and distinguishing statements play a central role in the interpretation and description of the factors, along side the explanations Q-sorters gave to the characterizing statements in their Q-sort. *P<0.01. **P<0.05.

The current study consisted of four phases. First, possible self-referent statements young adults can make about posttransplant health lifestyle were collected, through participant observation in the clinic and scientific literature. The statements should be matters of opinion only, not fact; Q-methodology assumes that opinions are subjective and can be shared, measured and compared [17]. A total of 72 statements were collected. Secondly, a broadly representative subset of statements was selected using the WHO dimensions of adherence [26]: socioeconomic-related factors, health care team- or health system-related factors, condition-related factors, treatment-related factors and patient-related factors. This was done by the authors, based on an iterative procedure and consensus. The final Q-set consisted of 37 statements (Table 1), which were randomly numbered and printed on cards.

Third, respondents were recruited and Q-sort interviews were conducted. All kidney transplant patients in our outpatient clinic, aged between 18 and 25 years (January 1st 2006), were invited to participate in this study (n=46). Those with a failed kidney graft were included to prevent bias toward compliant patients without graft loss. Patients were not selected, but we excluded two patients with an intellectual disability (n=44). In total 26 young adults responded (response rate of 59%). The main reason for nonparticipation was travel distance to the clinic. Other young adults had no interest in this research arguing they did not want to be reminded of their disease. Patient characteristics are shown in Table 2.

Table 2 Patient characteristics

	Q-study		
	Respondents (n=26)	Non-respondents (n=20)	Follow-up (n=34)
Age, median (range)(yr)	22.5 (18-25)	22 (18-25)	22.5 (18-25)
Time after transplantation, median (range)(yr)	2.5 (0-17)	5.5 (0-17)	3(0-19)
Gender			
Female	10 (38.5%)	6 (30.0%)	10 (29.4%)
Male	16 (61.5%)	14 (70.0%)	24 (70.6%)
Graft			
Functioning	22 (84.6%)	18 (90.0%)	32 (94.1%)
Failure	4 (15.4%)	2 (10.0%)	2 (5.9%)
Education			
High	8 (30.8%)	n.r.	n.r.
Middle	8 (30.8%)		
Low	10 (38.4%)		
Ethnicity			
Caucasian	19 (73.1%)	16 (80.0%)	21 (61.8%)
Other	7 (26.9%)	4 (20.0%)	13 (38.2%)
Living environment			
Independent	9(34.6%)	n.r.	n.r.
With parents	17(65.4%)		

There were no statistically significant differences between respondents and nonrespondents for age, gender, functioning graft, or ethnicity. All one-to-one interviews were conducted by a trained nurse practitioner (M.T.) in a private room in the outpatient clinic at the hospital. During the interview, participants were asked to rank-order the 37 cards containing the statements, using a score sheet (Fig. 2). They were first asked to read through all statements and to sort them into three piles: cards containing statements with which they agreed, disagreed, and had no opinion about or were considered irrelevant. Next, they were instructed to take the pile with cards they agreed with, read through them again, and to select the two they agreed with most. These were placed in the two spots at the extreme right of the score sheet (Fig. 2). From the remaining cards in the pile they selected the four they agreed most with, et cetera, until all cards in the pile were placed on the score sheet. These steps were repeated for the pile with cards they disagreed with, now working from the left of the score sheet. Finally, the cards in the last pile were rank-ordered in the remaining spots on the score sheet, as felt suited by the respondent. At the end of the interview, participants were asked to reflect on their rank-ordering of the statements and to motivate their preferences. The interviews were audio-taped and transcribed. Finally, the data were analyzed and interpreted. The individual rankings of statements were analyzed using common factor analysis (extraction method: centroid/rotation method: varimax). Q-analysis differs from conventional factor analysis only in the sense that the Q-sort(er)s are taken as variables. Consequently, respondents are clustered according to (dis)similarity in their ranking of the statements, and the resulting factors represent clusters of young adult transplant recipients who share a posttransplant attitude about their health lifestyle. For each factor a composite sort was calculated, which is a weighted ranking of the statements based on the underlying Q-sorts and their correlation coefficients with the factors as weights. This composite sort represents how a young renal transplant recipient correlating 100% with that factor would have rank-ordered the statements, and is the basis for interpretation and description of the factor. Data were analyzed using PQMethod 2.11 (software and manual are available at www.qmethod.org or www.rz.unibw-muenchen.de/p41bsmk/qmethod).

Then, as a first test of these results as a potential screening instrument, a convenience sample of 34 young renal transplant recipients categorized themselves on the factors: six patients who had recently been transplanted (between January 2006 and April 2007), three patient who came from the pediatric department, 19 respondents from the main study (of whom 12 loaded on one of the four factors), and six nonrespondents from the main study who agreed to participate in the follow-up. For this purpose, four short factor descriptions were developed, highlighting the important distinguishing characteristics of each attitude profile (see Table 1). These 34 young adults were asked how well each of the factor descriptions fitted them, using a 5-point Likert scale ranging from “totally not” to

"very well". This was done in an interview setting, by the same trained nurse practitioner (M.T.) during a regular visit to the same outpatient clinic in the period January to April 2007. Spearman correlations were computed to assess discriminate validity.

The study was approved by the Medical Ethics Review Committee of the Erasmus University Medical Center of Rotterdam.

Results

Twenty-six young renal transplant recipients (18-25years) participated in the study. We observed that they were willing to discuss sensitive topics in response to the statements printed on the cards. Analysis of their Q-sorts resulted in a four factor solution, that is, four distinct young adult posttransplant health lifestyle attitude profiles (Table 1). The four factors were defined by 17 participants (65%); four participants did not load statistically significantly on any of the factors and five participants were confounded.

Young adults loading on the first factor (a) worry that their kidney will be rejected (statement 2 gets a +3 score; Table 1), are concerned about their future (statement 20), and think it is important that the outpatient clinic monitors their kidney function regularly (statement 34). Like someone said: "I wish I could see a doctor every week instead of once in two months" or "If I feel something different, I am scared that my kidney will reject." They are careful about their medication (statement 18, 27) and their health behavior (statement 36), and find it more important to be adherent than to have a good life now (statement 26). The post-sort interview indicated that these young adults prefer to be in control of their regime, but also wish to be monitored regularly by professionals. Non-adherence leads to feelings of guilt, and the regime and their prospects make them at higher risk of depression and gloominess than other groups. Factor (a) was labeled "concerned & controlled".

Young adults loading on the second factor (b) are appearance-orientated (statement 11 and 21), "I can't control my weight, due to the medication, that affects me a lot," do not wish their life to evolve around their disease (statement 35), and believe that after transplantation they can live a normal life (statement 19 and 31). They do not tell others they are transplanted (statement 1). "I never tell someone I have a transplant." Young adults with this attitude most fear being transplanted may interfere with getting into a normal relationship (statement 10), "Dialysis is at some point inevitable, a partner should know that," and feel least guilty about behaving unhealthily (statement 36). The risk for non-adherence seems relatively small in these young adults, but the fear for cosmetic side-effects of immunosuppressants, and the tendency to be incommunicative about their transplant in their social environment, may interfere with adherence to their regime in some occasions. Factor (b) was labeled "appearance-orientated".

Young adults loading on the third factor (c) believe strongly about not wanting to go back on dialysis again (statement 9) "I never want to go back (on dialysis), I can't maintain all those rules," and do not wish their life to evolve around their disease (statement 35). They feel they can live a normal life (statement 31), do not feel less fit than their peers (statement 14), do not seek contact with other transplant recipients (statement 23), are not afraid about getting into a relationship (statement 10), and are rarely gloomy or depressed (statement 30). These young adults appear pretty well informed about the medication they take (statement 25), think it is important that the outpatient clinic monitors their kidney function regularly (statement 34), and indicate that health care professionals should confront them if they do not adhere to their regimen (statement 28). They seek a normal life, with the least possible limitations from their regime. More than in other groups, these young adults are scared of a former rejection because of nonadherence and, although they try to comply better now, think it is important to be monitored by professionals. Factor (c) was labeled "opinionated & independent".

Finally, young adults loading on the fourth factor (d) find it more important to live a good life now than to be compliant (statement 26), find it hard to say no to friends (statement 17), and think nothing bad will happen if they forget their medication (statement 29). "When I don't take that pill I will not die, I'm not that punctual with my medication." Although they have no problems telling others they are transplanted (statement 1), they, least of all, believe they can live a normal life after transplantation (statement 31), least of all think it is important that the outpatient clinic monitors their kidney function regularly (statement 34), and most of all indicate to experience side effects (statement 24). In addition, they are not at all concerned about going back on dialysis (statement 9) and do not worry that their life evolves around their disease (statement 35). These young adults seems to be uninformed or uninterested in their illness and regime, and not to foresee or accept the risks of their nonadherent behaviour. Their risk for nonadherence therefore is high. Like one of them quoted: *"I know I am a kidney transplant patient, I know that some day I will probably become so ill that I can die within a week. So for now, I want to try it all."* Factor (d) was labeled "easy going & pliable".

In the follow-up analysis, we tried to identify the population at risk for non-adherence; therefore, we asked 34 young adult transplant recipients how well the four posttransplant health lifestyle attitudes suited them (patient characteristics; Table 2). Discriminating answers were obtained from 23 of 34 respondents (67%): nine respondents self-selected as attitude concerned and controlled, two as attitude appearance-orientated, nine as attitude opinionated and independent, and three as attitude easy going and pliable. The remaining respondents provided non-discriminating answers by eliciting equal highest scores on more than one item. We found two attitude scores to be correlated: a sizeable (.46) negative

correlation between the scores for attitudes concerned and controlled and easy going and pliable ($p<0.01$). In this relatively small sample, girls (4.2 vs. 3.0; $p<0.05$) and younger patients ($\rho = -.35$; $p<0.05$) scored higher on the attitude concerned and controlled. No statistically significant differences were found for the age at transplant and living or deceased donor kidney.

Finally, we can compare the results for young adults who participated in both studies: 12 of these 17 respondents loaded on one of the four factors in the Q-methodological study and self-selected one of the four profiles. Of the three respondents loading on the factor concerned and controlled in the Q-methodological study, two indicated that the description fitted them well in the follow-up exercise, and one very well. Of the two respondents loading on appearance orientated, one self-selected as fairly well and one as very well. Of the six loading on "opinionated and independent", one self-selected as not really, two as fairly well, one as well, and two as very well. Finally, the one loading on easy going and pliable self-selected as very well in the follow-up exercise. The results of both studies therefore seem fairly similar.

Discussion

This Q-methodological study revealed four distinct health lifestyle attitudes among young adult transplant recipients: (a) concerned and controlled, (b) appearance orientated, (c) opinionated and independent, and (d) easy going and pliable. The primary differences and similarities between these four attitudes have been discussed.

Some remarks need to be made regarding these results, however. First, unexpectedly, parents do not seem to play a significant role in any of the attitudes. This differs from former-related research among adolescents with chronic disorders in the Netherlands, which revealed a distinct attitude profile for their parents supporting and even taking over control of their regime [27]. This difference probably relates to the older age of our participants. In the present study, peers seem much more influential on posttransplant health lifestyle attitudes. Unfortunately, from the perspective of treatment adherence, peers had not a beneficial influence, especially in the case of young adults with attitude (d). Second, appearance is a hot topic in all attitudes, though most explicit in attitude (b). This concern seems mainly related to social acceptance by peers and the ability to get into relationships. The strongest implication to be considered in clinical practice is adherence to immunosuppressive drugs with cosmetic side-effects. Third, attitudes (a), (b) and (c) seem positively associated with adherence, but at least in two of them, (b) and (c), the need for monitoring by professionals is emphasized. This indicates that these young adults acknowledge the importance of adherence, try their best to comply, but still are unsure or would appreciate feedback on

how they are doing. Young adults with attitude (d) also emphasize the need for monitoring the functioning of their kidney by professionals, especially to be informed about the extent of the negative side-effects of their nonadherent behaviour. Finally, while depression previously has been indicated as a risk factor for nonadherence [12], here – in attitude (a)– we found the opposite. The gloominess of these young adults seems to be associated with the regime and their prospects, but translates into need for high control and monitoring than nonadherence.

Some remarks also need to be made regarding the methodology applied in this study. First, the sorting of the cards was perfectly feasible for these young adults and the postsort interviews indicated that they comprehended the task and the contents very well. In that sense, the postsort interview also served as a validity check, because incongruence between the sorting of the cards and explanations of the sort could be remedied. Either statements could be re-shifted on the score sheet in case they were misunderstood, or the explanation could be clarified to the interviewer. But this was rarely necessary, which is an indication for the validity of the results. This may also be helped by the fact that the principal investigator (M.T.) was familiar to the patients. The participants appeared open and frank about their behavior and underlying motivations, and did not experience the interview as an infringement on their privacy.

Second, we found the statements were of help in communication with these young adults. Adolescents are more vulnerable and less approachable for various psychological reasons [16]. Strikingly, young adults were talking easily about sensitive issues when confronted with the task to rank-order statements on a card, because it helped them raise issues they had not thought of or were reluctant about before. One of the participants even asked if he could have the cards so he could communicate better with his family about the different subjects coming with his disease. Participating in the study was not only enjoyable, but even empowering for participants. On the other hand, it is important to realize that this study was conducted among a small population in a single center. Although the size of our population is no worry to Q-methodology, we would applaud replication of this study in other centers.

The results of the follow-up exercise in which participants self-selected their factor membership using concise factor descriptions were promising. The discriminant validity was fair: 67% of respondents could be assigned to a single attitude, and we observed low correlations between attitude scores and in expected directions. In addition, the congruence between factor membership in the Q-methodological study and self-selection in the follow-up study among 12 respondents who participated in both was good. All in all, most participants seem to be able to distinguish themselves using such short profile descriptions, possibly better than they would in a direct interaction with a healthcare professional. Therefore, self-selection can support the quality and efficiency of patient-

professional interactions. It may help as a first screening tool concerning adherence, as a means to direct the communication, and a way to help tailor the regime to the needs and concerns of patients. However, to determine the prevalence of these attitudes within this population and how this affects graft survival, conventional survey analysis using a larger, representative sample of patients is required.

Nevertheless, in our outpatient clinic the process and results of this Q-methodological study have been experienced as informative and contributing to patient-oriented care. Although the value of the results as a screening tool remains to be investigated, the Q-sorting exercise and the self-selection exercise have proved to be helpful in increasing the interaction with this sometimes difficult and incommunicative group.

References

1. Eris J. Clinical experience with Everolimus (Certican) in Young Renal Transplant Recipients. *Transplantation* 2005; 79:89-92
2. Loghman-Adman M. Medication Noncompliance in Patients With Chronic Disease: Issues in Dialysis and Renal Transplantation. *Am J Manag Care* 2003; 9:155-171
3. Tielen M, Zuidema W, IJzermans J, Weimar W. Mothers should think twice before donating a kidney to their adolescent sons (Abstract). *Tranplant Int* 2005; 18, (Suppl 1): 48
4. Oniscu GC, Brown H, Forsythe JL. How Old is Old for Transplantation. *Am J Transplant* 2004; 4:2067-2074
5. Meyers KE, Thomson PD, Weiland H. Noncompliance in children and adolescents after renal transplantation. *Transplantation* 1996; 62:186-189
6. Nevins TE, Matas AJ. Medication noncompliance: another iceberg's tip. *Transplantation* 2004; 77:776-778
7. Russell CL, Conn VS, Ashbaugh C, Madsen R, Hayes K, Ross G. Medication adherence patterns in adult renal transplant recipients. *Res Nurs Health* 2006;29(6):521-32
8. Rianthavorn P, Ettenger RB. Medication non-adherence in the adolescent renal transplant recipient: a clinician's viewpoint. *Pediatr Transplant* 2005;9(3):398-407
9. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant* 2005;9(3):381-90
10. Falkenstein K, Flynn L, Kirkpatrick B, Casa-Melley A, Dunn S. Non-compliance in children post-liver transplant. Who are the culprits? *Pediatr Transplant* 2004;8(3):233-6
11. Gerson AC, Furth SL, Neu AM, Fivush BA. Assessing associations between medication adherence and potentially modifiable psychosocial variables in pediatric kidney transplant recipients and their families. *Pediatr Transplant* 2004;8(6):543-50
12. Shemesh E, Lurie S, Stuber ML, Emre S, Patel Y, Vohra P, Aromando M, Shneider BL. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. *Pediatrics* 2000;105(2):E29
13. Shemesh E, Shneider BL, Savitzky JK, et al. Medication adherence in pediatric and adolescent liver transplant recipients. *Pediatrics* 2004;113(4):825-32
14. Shemesh E. Non-adherence to medications following pediatric liver transplantation. *Pediatr Transplant* 2004;8(6):600-5
15. Berquist RK, Berquist WE, Esquivel CO, Cox KL, Wayman KI, Litt IF. Adolescent non-adherence: prevalence and consequences in liver transplant recipients. *Pediatr Transplant* 2006;10(3):304-10
16. Feinstein S, Keich R, Becker-Cohen R, Rinat C, Schwartz SB, Frishberg Y. Is noncompliance among adolescent renal transplant recipients inevitable? *Pediatrics* 2005;115(4):969-73
17. Brown SR. A primer on Q-methodology. *Operant Subjectivity* 1993; 16:91-138
18. Brown SR. Q-methodology and qualitative research. *Qual Health Res* 1996;6(4), 561–567
19. Van Exel NJA, De Graaf G. Q-methodology: A sneak preview. Available at www.qmethodology.net and www.qmethod.org. 2005
20. Dennis KE, Goldberg AP. Weight control self-efficacy types and transitions affect weight-loss outcomes in obese women. *Addict Behav* 1996; 21:103-116
21. Cross RM. Exploring attitudes: The case for Q-methodology. *Health Educ Res* 2005;20(2), 206–213

22. Van Exel NJA, G de Graaf, WBF Brouwer. “Everyone dies, so you might as well have fun!” Images of youths about their health lifestyle. *Soc Sci Med* 2006;63(10): 2628–2639

23. Risdon A, Eccleston C, Crombez G, McCracken L. How can we learn to live with pain? A Q-methodological analysis of the diverse understandings of acceptance of chronic pain. *Soc Sci Med* 2003;56: 375–386

24. Valenta A.L., Wigger, U. Q-methodology: Definition and Application in Health Care Informatics. *J Am Med Assoc* 1997;4:501-510

25. Smith NW. Current systems in psychology: History, theory, research, and applications. Belmont, CA, Wadsworth 2001

26. WHO. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization; 2003

27. Staa AL van, Jedeloo S, Latour JM, van Exel NJA. Using Q-methodology to explore preferences for care of adolescents with chronic disorders: Four profiles, presented at the 25th International Congress of Pediatrics, 30th August 2007, Athens.

3

Immunosuppressive Drugs and Young Adults:

A Difficult Combination

M. Tielen[1], S. Jedeloo[2], A.L. van Staa[3], W. Weimar[1]

[1] Department of internal Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.
[2] Expert Centre Transitions in Care, Rotterdam University, Rotterdam, The Netherlands.
[3] Institute of Health Policy and Management, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

Published in book:
Organ Transplantation: Ethical, Legal and Psychosocial Aspects towards a Common European Policy, W. Weimar, M.A. Bos, J.J. Busschbach, Pabst Science Publishers ISBN 978-3-89967-415-6, 2008, 563-569.

Abstract

Background: In our center we encounter serious problems with a number young adult (18-25yrs) renal transplant recipients that are non-compliant to the medication regime. This could well be one of the reasons for the significantly worse unadjusted 10 years kidney graft survival in this patient group compared to that in recipients > 25 years: 47.2% versus 64.0%. This paper focuses on the attitudes and behavior of young adults towards compliance with the immunosuppressive drugs.

Method: We used Q-methodology to identify attitude profiles associated with noncompliant behavior. Adolescent renal transplant recipients (n=25) sorted a set of 37 statements (Q-set) along a continuum of preferences to reveal categories of individuals who shared common viewpoints. The same Q-set was also used as a topic list for an in-depth interview. In this paper, we focus on the interview results of four statements, related to compliance with immunosuppressive drugs. Each interview was fully written down, using the software program Atlas.Ti® for coding and labeling.

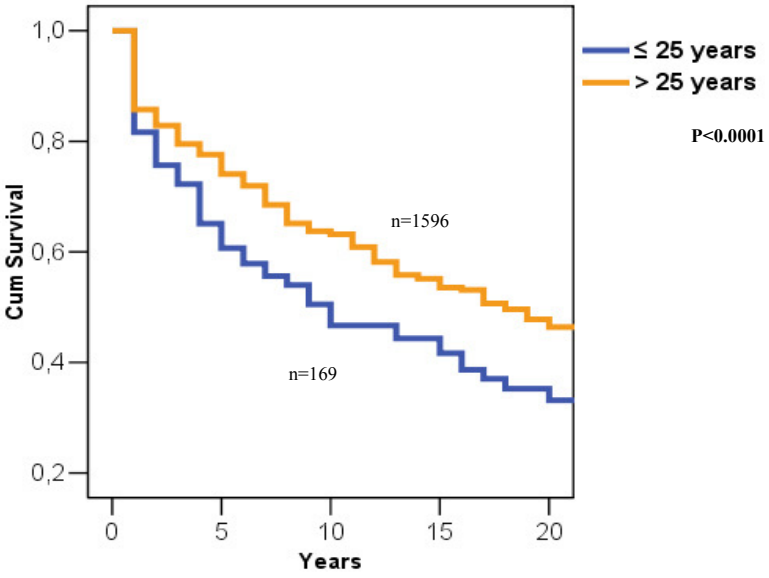
Results: Almost half of respondents (40%) think that forgetting medication will not lead to serious consequences. They feel they took so much medication over the years that they had developed a certain reserve immunity against rejection. Others state that they had become indifferent after experiencing that 'nothing happened' after forgetting their medication. Most adolescents declare having no problems taking their medication when going out with friends. They do not feel ashamed, but some lose track of time and simply forget taking medication when they are out with friends. Remarkably, 18 of the 25 young adults (72%) admit to not always taking their medication on time. When they sleep late, only 7 of them set the alarm clock in order to take their medication as prescribed.

Conclusion: Using the Q-set statements as interview topics triggered young adults to ventilate their opinion and reveal their medication practice. Confronting statements on cards appeared to be very useful in communicating with adolescents about difficult subjects such as noncompliance. This helps caretakers in the outpatient clinic to explore and discuss reasons for nonadherence to immunosuppressive drugs. Many young adults are not very accurate in taking medication on time, and 40% even think nothing bad will happen when they forget their immunosuppressive drugs. Healthcare professionals should be aware of this grossly underestimated problem.

Introduction

Young adults try to establish their identity and autonomy and want to be independent while at the same time they are dependent on the help from adults and healthcare professionals when they are chronically ill [1]. This struggle for independency in a situation of dependency often leads to non-compliance which may result in graft rejection. In our experience, non-compliance is a major problem in young adult patients. In our outpatient clinic we often see young male adults who appear indifferent and careless, whom we sometimes call 'the baseball caps'. The impact of non-compliance is more obvious in adolescent transplant recipients than in the older transplant population. We analyzed renal graft survival of all our kidney transplant patients between 1971-2005. We stratified them according to age: older and younger than 25 (Fig.1).

Figure 1 Graft survival censored for death of all kidney transplants performed in Rotterdam from 1971-2005



We found, as has also been suggested in literature, a significant worse graft survival for young adults compared with older adults [2,3,4]. While young adults may have a more vigorous immune system resulting in more rejection [5], this is probably not the only explanation. Non-adherence can also be a cause of late graft loss [1,6,7]. In a previous study we used Q-methodology to identify 4 behavior patterns in young adults [8]. These four profiles are A; Concerned & Controlled, profile B; Appearance orientated & Uncommunicative, profile C; Opinioned & Independent and profile D; Easy going & Pliable. The young adults in profile A have the lowest risk of noncompliance and the young adults in profile D have the highest

risk. One of the key issues in non-compliance concerns proper taking of immunosuppressive drugs as prescribed. Therefore, in this paper we focus on the ideas of young adults regarding this sensitive topic.

Methodology

The goal of Q-methodology is, first and foremost, to uncover different patterns of thought (not their numerical distribution among the larger population) [9,10]. Q-methodology exists of three stages: first, to develop a set of statements to be sorted (called a Q-sample), second, to require participants to sort the statements along a continuum of preference, and last, to analyze and to interpret the data [11,12]. We made a list of 37 statements (Q-set). The statements are matters of opinion only, not facts. All statements are related to issues related to non-compliance. We followed the different dimensions of non-adherence described by WHO [13]. Adolescent renal transplant recipients (n=25) sorted the Q-sets along a continuum of preferences ('disagree most' to 'agree most') to reveal categories of individuals who shared common viewpoints. (Fig. see page 21).

Afterwards, we performed an in-depth interview about all the statements, using the statements as a topic list. We asked the respondent to comment on each statement. The interviews were recorded and later transcribed *ad verbatim*. For qualitative analysis, consisting of coding and labeling followed by thematic analysis using constant comparison, we used the computerprogramme Atlas.Ti®. This paper focuses on the responses to four statements concerning compliance to immunosuppressive drugs:

1. "If you forget your medication, nothing really bad will happen"
2. "I never forget my medication"
3. "When I stay in bed late, I just take my medication later"
4. "When I am out with friends, I am not very punctual with medication

Results

Patients' characteristics of the 25 participants are shown in table 1.

Table 1 Patient Characteristics (n=25)

Patient characteristics	Respondents
Age	18-25yrs
Sex	10 (40%) female/ 15 (60%) male
Graft	21 (84%) functioning graft/4 (16%) failures
Education level	8 (32%) high/ 8 (32%) middle/ 9 (36%) low
Ethnicity	18 (72%) Caucasian/ 7 (28%) others
Type of transplant	18 (72%) living donor kidney/ 7 (28%) deceased donor kidney
Living environment	9 (36%) independent/ 16 (64%) with parents

Ten recipients felt that forgetting medication would not lead to serious consequences (Table 2).

Table 2 Agree and disagree of the 4 statements

Statement	Agree	Disagree
"When you forget your medication nothing bad will really happen"	40% (n=10)	60% (n=15)
"I never forget my medication	48% (n=12)	52% (n=13)
"When I am out with friends, I am not very punctual with medication"	20% (n=5)	80% (n=20)
"When I stay in bed late, I just take my medication later"	72% (n=18)	28% (n=7)

One girl said: *"I did it a few times (forgetting medication) and nothing happened. I take my pills on Tuesday, Wednesday, Thursday and Friday, on Saturday I do not. And then I take them again"*. When asked if she wasn't scared her kidney would reject, she said: *"Sometimes I am scared because I think if I lose this kidney, I will regret that I did not take my medication".*

Some recipients thought that after taking so much medication over the past years, a certain reserve immunity against rejection had been developed. Others stated they had become indifferent after experiencing that *'nothing happened'* after forgetting their medication. One young man thought that, because he was prescribed a low dose of immunosuppressive drugs, he could more easily forget his medication than someone who needed a higher dose of immunosuppressants. Two of the eight young men who all disagreed with the statement "when you forget your medication nothing bad will really happen" had learned this the hard way; one went through an acute rejection from which he fully recovered and the other had experienced graft loss due to non-compliance. From the ten recipients who admitted to non-compliance, five had received a deceased donor- and five a living donor kidney.

In contrast, the responses to the statement "I never forget my medication", were quite different. Half of the respondents (48%) stated that they never forget their medication. They are so used to take medication, a girl said: "*I can't imagine how people can live without any medication, I have medication everywhere, in the car, with friends, if I forget, then I have them everywhere".* But half of the interviewed forget their medication sometimes, however not intentionally: they are too occupied or in a hurry. One young man, who sometimes forgets his medication, says he does not feel like taking medication at that time and then simply forgets. Another one states: *"When I forget my medication, I am really angry [with myself], when it happens twice a week I think it goes really bad and I have to focus more".* One respondent thinks it is important to take his medication since he received a transplant kidney. When he was still on dialysis he intentionally forgot his medication, because he did not feel like it and did not see the point of taking medication all the time. Most adolescents say they have no problem taking medication when going out with friends (80%). They claim not to feel ashamed, but some lose track of time and simply forget taking medication when they are out with friends. A young man explained it was hard to remember his medication

when he was on holiday with friends, because there was '*no structure'*. But a young woman said: *"You do crazy things when you are on holiday, but I always take care of my kidney, even when I drink a lot of alcohol, I think about my kidney, you never forget your kidney".*

Remarkably, 18 of the 25 young adults (72%) admit to not always taking their medication on time (Table 2). Especially after going out with friends the day before, they forget to take their medication on the prescribed time. Only seven respondents claim to set the alarm clock when they are sleeping late, in order to take their medication as prescribed. After taking the pills, they go back to sleep. One girl said she took her medication regularly when admitted to hospital, but when at home, she preferred to look at a television program and postpone her medication with one or two hours. Especially during the weekend young adults experience problems with the regular intake of immunosuppressive drugs. A girl said: *"In the past, my parents used to wake me up. I was always mad because of that, nowadays I do it myself, but I don't care to take the medication later"*.

Discussion

To better detect and understand non-compliance, Q-methodology was used to gather information about various issues regarding non-compliance. After the sorting of the cards with statements (Qset), young adults were asked to give their opinion about each statement. Statements in the middle had a 'neutral' meaning for them (issues not so important to young adults as compared to the other issues on the cards put at the extremes). Remarkably, these neutral statements turn out to be of special interest to healthcare professionals. Rianthavorn and Attenger described a group of *invulnerable* non-compliers, i.e. recipients who don't think that missing medication can hurt them [1]. They feel invulnerable to the effects of discontinuing of immunosuppressive drugs. In our study, we found a similar group of *invulnerable* non-compliers. The statement: "Forgetting medication will not lead to serious consequences" turned out to be a distinguishing and characteristic statement in Q-profile D, the most non-compliant group [8]. In contrast, almost every young adult put the card with the statement: "When I sleep till late, I just take my medication later" in the middle, neutral zone. The interview afterwards revealed that young adults think it is normal to take medication much later when they sleep late. Russel et al. also discovered patterns in patients who take medication later or missed a dose [14]. Apparently, young adults are not too accurate with the medication, especially when it does not fit in with their life style and with important social activities such as going out with friends. Adolescents are more vulnerable and less approachable for various psychological reasons [15].

Strikingly, young adults were willing to talk easily about sensitive issues when confronted with statements on a card. The interviewer in this study (M.T.) is a nurse practitioner familiar

with and also slightly older then the respondents. This could, on theoretical grounds, be a disadvantage because of a possible infringement on their privacy. However, we feel it turned out to be an advantage, as the respondents felt comfortable with her, which resulted in frank answers.

Conclusion

Q-methodology was used to create attitude profiles among young adults. In this study, we discovered that using these statements as interview topics proved to be of great help in communication with adolescents. The cards triggered them to ventilate their opinion and reveal their ideas and their medication practices. This is extremely relevant for healthcare professionals in their attempt to understand the motivation of young adults. Discussing these sensitive issues may very well help young adults to better comply with their strict medication regime. Many young adults are not very accurate with taking medication on time, and a lot of them think nothing bad will happen if they forget their immunosuppressive drugs. Healthcare professionals should be aware of this grossly underestimated problem.

References

1. Rianthavorn P, Ettenger R.B., Medication non-adherence in the adolescent renal transplant recipient: A clinician's viewpoint. Pediatric Transplantation 2005; 9:398-407.
2. Tielen M, Zuidema W, IJzermans J, Weimar W, Mothers should think twice before donating a kidney to their adolescent sons, Tranplant. Int (2005) 18, Supplement 1, 48 (Abstract)
3. Eris. J. Clinical experience with Everolimus (Certican) in Young Renal Transplant Recipients. Transplantation 2005; 79:89-92.
4. Oniscu G., Brown H., Forsythe J.L., How Old is Old for transplantation? American Journal of Transplantation 2004; 4:2067-2074.
5. DeVeale B., Brummel T., Seroude L., Immunity and aging: the enemy within? Aging Cell 2004 3(4); 195-208.
6. Nevins TE, Matas AJ. Medication noncompliance: another iceberg's tip. Transplantation 2004; 77:776-778.
7. Loghman-Adman M., Medication Noncompliance in Patients With Chronic Disease: Issues in Dialysis and Renal Transplantation. The American Journal of managed care 2003; 9:155-171.
8. Tielen M, van Staa A.L., Jedeloo S., van Exel N.J.A., Weimar W., "If you forget your medication once in a while, nothing really bad will happen!" An investigation of adolescent renal transplant recipients at risk for non-compliance using Q-methodology 2007 (submitted for publication)
9. Valenta A.L., Wigger, U., Q-methodology: Definition and Application in Health Care Informatics. J Am Med Assoc. 1997;4:501-510.
10. Van Exel NJA, De Graaf G. Q-methodology: A sneak preview [available from www.qmethodology.net and www.qmethod.org]. 2005
11. Brown SR. Q-methodology and qualitative research. Qualitative Health Research 1996;6(4), 561–567
12. Brown SR. A primer on Q-methodology. Operant Subjectivity. 1993; 16:91-138.
13. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
14. Russel C.L., Conn V.S., Ashbaugh C., Madsen R., Hayes K., Ross G. Medication Adherence Patterns in Adult Renal Transplant Recipients 2006 Research In Nursing & Health 29;521-532.
15. Feinstein S., Keich R., Becker-Cohen R, Rinat C., Shepard B., Schwartz and Frishberg Y. Is Noncompliance Among Adolesent Renal Transplant Recipients Inevitable? Pediatrics 2005 115;4:969-973.

4

Attitudes towards medication non-adherence in elderly kidney transplant patients: a Q-methodology study

Mirjam Tielen[1], N. Job A. van Exel[2], Marleen. C. van Buren[1],
Louise Maasdam[1] and Willem Weimar[1]

[1] Department of Internal Medicine, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
[2] Institute of Health Policy and Management (iBMG), Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

Nephrology Dialysis Transplantation 2011; 26(5): 1723-1728

Abstract

Background: Non-adherence to the post-transplant regime is a common problem in kidney transplant patients and may lead to rejection or even graft failure. This study investigated attitudes towards the post-transplant regime of immunosuppressive medication among the ever growing population of elderly kidney recipients.

Methods: Q-methodology was used to explore attitude profiles. Participants (>65yrs) were asked to rank-order opinion statements on issues associated with (non)-adherence. The rankings were subject to by-person factor analysis, and the resulting factors were interpreted and described as attitudes.

Results: Twenty-six elderly renal transplant recipients participated in the study. All passed the Mini-Mental State Examination. Two attitude profiles were found: (i) satisfied and easy-going (attitude A), and (ii) reserved and concerned (attitude B). Elderly patients with attitude A want to enjoy the new life following their kidney transplant, are not very concerned about having to recommence dialysis, now and then even forget their regime, but do not really worry about it. Elderly patients with attitude B feel more insecure about their kidney transplant, are fairly concerned over issues like rejection or going back on dialysis, and try to adapt their way of life to the regime. One-third of these elderly patients forget their medication at least once a month, but there was no difference between attitude groups.

Conclusions: Attitudes about the post-transplant regime differ among elderly patients, implying different needs for assistance, monitoring and risk of non-adherence to the regime. The proportion of elderly that forgets their medication is considerable, but may be much higher among those with mild and severe cognitive limitations.

Introduction

Kidney transplantation is the optimal treatment for end stage renal disease. Life expectation is significantly improved among transplant patients compared to that of the age-matched wait-listed patients on dialysis (1-5). Also elderly patients may benefit as they experience a better quality of life after transplantation compared to dialysis treatment (6). Therefore the number of transplanted elderly patients is increasing. At the same time we are not informed how elderly view their post transplant lifestyle. Moreover still little is known about their adherence to the medication regime. Non-adherence has been shown to be related to rejection and even graft failure (7-10). Non-adherence to medication is a common problem in young kidney transplant patients, but this issue has yet to be studied in elderly transplant recipients. Risk factors of non-adherence are depression, less structure in daily life and social isolation (11). We hypothesized that these risk factors are likely to play an important role in adherence among the elderly population. Also other problems specific to the elderly may also interfere with medication adherence e.g. label-reading and interpretation, child-resistant containers and short-term memory (12). Non-adherence to immunosuppressive medication may add to older age related risk factors such as cardiovascular complications and psycho geriatric morbidity. The way in which patients think about their medication and lifestyle is suggested to be linked to their behavior. It is supposed that attitudes are concealed and not directly observable in themselves, but they cause actions and behaviors that are observable, i.e. health-related behaviors (13). The present study investigated elderly kidney transplant recipients' attitudes towards their post-transplant immunosuppressive medication regime. This study is comparable to a similar study conducted among young renal transplant recipients (10). We expected to discover a limited number of attitude profiles specific for elderly transplant patients that would be related to medication taking behavior and ultimately to adherence. Understanding patients' perspectives might help predict health behaviors and implement more effective interventions.

Subjects and Methods

Q-methodology was used to investigate attitudes towards post-transplant health lifestyle. Participants are presented with a sample of opinion statements and are asked to rank-order these statements according to the extent to which they agree with the statement. The individual rankings of statements are subject to by-person factor-analysis so as to reveal corresponding patterns in the way the statements were ranked by respondents. The results of a Q-methodological study can thus be used to describe a population of viewpoints, not a population of people (14). Q-methodology emphasizes the qualitative 'how' and 'why'

people think the way they do, but does not count 'how many' people think a certain way. For this purpose, Q methodology does not need large numbers of subjects (15,16).

The current study consisted of four phases. First, self-referent statements that elderly patients can make about post-transplant health lifestyle were collected through interviews with elderly transplant patients, observations in the clinic and studying the literature (10). The WHO defined different dimensions of non-adherence (17): socioeconomic-related factors, health care team or health system-related factors, condition-related factors, treatment-related factors and patient-related factors. The second step was therefore to categorize the collected statements according to these dimensions by experts and condense them to a manageable set for the population under study. Statements were chosen that represented the pertinent issues within each dimension. The final set consisted of 35 statements (Table 1) that were randomly numbered and printed on cards. Many studies have indicated that depression is a risk factor for non-adherence (7,11,18,19). Therefore we have included statements 1, 2 and 5, that we used as indicators of depressive symptoms in the Q-set (Table 1).

Third, all patients who had been transplanted at the department of Internal Medicine, Erasmus MC, had received their transplant after their 65th birthday, and with a follow up of at least one year, were selected to participate in this study (n=72). We included only these patients because they experienced this major life event at an older age. Of these, 46 patients had an outpatient clinic appointment during the period of inclusion and were therefore invited to participate. The other 26 patients were not invited because they had no appointment during the study period or some (n=5) were lost to follow up. In total 26 elderly patients of the 46 who were invited to participate, responded (response rate of 56.5%). The main reasons for non-participation were limitations in vision or hearing impeding participation in the study, and children of the elderly declining participation of their parent because of admission to a nursing home or cognitive limitations. The characteristics of participants are shown in table 2. There were no statistically significant differences between respondents and non-respondents in age, gender, or ethnicity.

Table 1 Statements and factor array

Statements	Post transplant lifestyles	
	Satisfied and Easy-going	Reserved and Concerned
1. I feel lonely	-2**	-1
2. I think a lot about death	0*	-1
3. I am happy with my new kidney	+3	+3
4. I am worried that my kidney will be rejected	-1**	+3
5. I often feel gloomy and depressed	-3**	-1
6. I'm scared I will have to go back on dialysis again	-2**	+2
7. I feel guilty if I do something that is not so healthy	0	0
8. I should never have had this kidney transplant	-3	-3
9. I am sometimes forgetful	+1*	0
10. Other people sometimes think that I'm forgetful	0*	0
11. I am able to prepare and take my medication myself	+1	+1
12. I know why I have to take these medication for	+1	+1
13. I would appreciate more information about my transplantation	0	0
14. If you forget your medication once in a while, nothing really bad will happen	0**	-3
15. I don't want my life to evolve around my disease	+2**	+1
16. When I stay in bed late, I just take my medication later	+1**	0
17. After the transplantation I can do everything normally again	+2**	0
18. I would rather not tell others that I have been transplanted	0	0
19. Other people sometimes think that I complain about how I am doing	-1*	-1
20. I receive enough support from friends and/or family	+1	+1
21. I feel more tired than my peers	0	+1
22. I would appreciate meeting with other elderly kidney transplant patients	0*	-1
23. I do what the doctors tell me, they know what is best for me	+2	+2
24. I miss the companionship of the dialysis ward	-1*	-2
25. I have a lot of confidence in my doctor	+2	+2
26. In the clinic they treat me like an infant	-2	-2
27. I don't understand what the doctor says because he uses difficult words	-2	-2
28. I am not changing my health lifestyle because a doctor wants me to	0**	-1
29. I find it reassuring that they check my kidney function regularly at the outpatient clinic	+3	+2
30. Traveling to the hospital costs me a lot of energy	-1*	0
31. I sometimes forget my medication	+1**	-1
32. I have problems swallowing larger pills	-1	0
33. I have side-effects from my medication	-1**	+1
34. A pillbox is a handy aid	+1	+1
35. If I'm not sure whether I have taken my pills already, I just take it again	-1	-2

A '-3' score indicates that a typical elderly with that health lifestyle attitude would disagree most with that statement, a '+3' score indicates that (s)he would agree most.
*P<0.05; ** P<0.01.

Table 2 Patient characteristics

Patient characteristics	Respondents (n=26)	Non-respondents (n=20)
Age (years)	67-82 (median 73)	67-84 (median 72,5)
Time after transplantation (years)	1-10 (median 5)	1-16 (median 4,5)
Gender	5 F / 21 M	7 F / 13 M
Education level	1 university, 5 high, 2 middle, 18 low	Unknown
MMSE score	25-30 (median 29)	Unknown
Ethnicity	Caucasian	16 Caucasian, 3 Asian, 1 African
Kidney transplant	14 living/ 12 post mortal	11 living/ 9 post mortal
Living status	All living independently	Unknown
Civil status	21 married/ 2 single/ 3 widowed	Unknown

All interviews were conducted in a private room in the outpatient clinic. During the interview, participants were asked to rank-order the 35 cards containing the opinion statements, using a score sheet (figure, page 21).

Furthermore, as a way of checking for completeness of the statement set, respondents received two additional blank cards on which they could indicate an aspect they missed in the set; these cards could be ranked at the bottom of any of the columns of the score sheet. In post-sort interviews participants were asked to explain the reasoning behind their choices, in particular the cards positioned on the extreme ends of the score sheet.

Finally, in phase four, the data was analyzed and interpreted. The individual rankings of statements were analyzed using common by-person factor analysis (extraction method: centroid; rotation method: varimax). Data were analyzed using PQMethod 2.11 (dedicated software and manual are available via http:///www.rz.unibw-muenchen.de/p41bsmk/qmethod). The resulting factors represent clusters of elderly transplant patients whose attitudes about their post-transplant health lifestyle are similar.

Q-methodology is an established method that can be used to study subjectivity in a systematic way, such as peoples' viewpoints, beliefs, and attitudes (20,21). It combines the strengths of qualitative and quantitative research, and is regarded a more robust technique than alternative methods for the measurement of attitudes and subjective opinion (13, 22).

Mini-Mental State examination

All 26 patients were asked to complete a standardized mini mental state examination (23). Patients scoring less than 25 points (of the maximum attainable 30 points) were considered cognitively unable to participate in the study.

Self-reported non-adherence

All respondents answered four questions of the Siegal Scale (24), in order to assess adherence to immunosuppressive drugs during the last month and the reason why they were non-adherent (25). In a non-accusatory, information seeking way participants were asked how often they (i) had not taken their immunosuppressive drugs (IS), (ii) had forgotten to take their IS, (iii) had not taken their IS because they believed that they did not need them and (iv) had reduced the prescribed amount of IS. Frequency of these factors was measured using a 7-point scale ranging from 0 (never) to 6 (daily). Patients answering "never" were considered to be adherent. All other scores (i.e. once a month, twice a month, three times, or more) indicated non-adherence with medication taking. To test convergent validity a Pearson's' correlation was conducted between the Siegal scale and the following statements: "I sometimes forget my medication", "When I stay in bed late, I just take my medication later", and "If I'm not sure whether I have taken my pills already, I just take them again" [statements 16, 31, and 35 in table 1].

Results

Twenty-six elderly kidney transplant recipients (67-82 years) participated in this study. All participants were included because they had a MMSE score of ≥25; median score was 29. Analysis of their Q-sorts resulted in a two factor solution (Eigen value > 1), indicating there were two distinct post-transplant health lifestyle attitudes (Table 1). Twelve elderly patients defined factor 1 and 14 elderly patients defined factor 2.

The elderly patients who defined the first factor were not worried that their kidney will be rejected (statement 4; see Table 1) but nonetheless think it is important that their kidney function is monitored regularly (statement 29). If dialysis is necessarily, they are not afraid of it (statement 6). They are sometimes forgetful (statement 9), but are not concerned about the consequences of forgetting their medication once in a while (statement 14), and take their medication later if they sleep late (statement 16). They do not evidence signs of depression (statements 1, 5), do not want life to revolve around their disease (statement 15) and are of the opinion that after transplantation they can lead a normal life (statement 17). They experience few side effects of their medication (statement 33). This factor was labeled "Satisfied & Easy-going". The post-sort interviews indicated that these elderly patients are satisfied with the new life that was made possible thanks to their kidney transplant. They find it important to have their kidney function checked regularly, to confirm that they are doing well. They tend to forget their medication now and then, but don't make a big deal or feel guilty about it. The following quotes illustrate this attitude profile: "I sometimes think I don't need my medication and I would like to try not taking them" and "I don't mind

forgetting my medication, I would like to have less medication anyway". Another respondent said: "Sometimes I take my medication later, the nurses did not give me a hard time when I forgot, so why should I mind".

The elderly patients who defined the second factor were worried that their kidney could be rejected (statement 4) and were afraid of going back to dialysis (statements 6, 24). They were of the opinion that forgetting medication will have harmful consequences for them (statement 14), but also indicated that they experienced some negative side effects from their medication (statement 33). These elderly patients appeared less happy and comfortable with their post-transplant life than the elderly in the other factor (statements 1, 5, 17), and generally felt more tired than their peers (statement 21). They were more sensitive to their doctor's opinion about their health lifestyle (statement 28). This factor was therefore labelled "Reserved & Concerned". The post-sort interviews confirmed these findings. These elderly patients did not want to go back on dialysis, "It was horrible to lay there for four hours". Some of these elderly said they would rather die than go back on dialysis, but at the same time contemplated that they might change their opinion if this happened, depending on their partner still being alive. Because they worried about the consequences of forgetting their medication, they tried to be accurate ("I had a clock for my medication, when it was broken it was really hard for me") and compliant to their doctor's advice ("My doctor is my teacher, so I change something if he thinks that is necessarily"). Based on this combination of attitudes we would expect adherence to be high among these patients.

We observed consensus about several issues between elderly patients with the two different attitudes. Firstly, elderly patients trusted and had a lot of faith in their doctor, and were satisfied with the way they are treated by hospital staff (statements 23, 25, 26, 27). In addition, despite the some worries, all elderly seemed happy with their kidney transplant (statements 3, 8). One respondent for instance said: "If I would need another kidney transplantation tomorrow, I would not hesitate". Finally, social isolation was not a serious issue in these elderly patients, and they appreciated the support they got from friends and family (statement 20). Almost all patients (n=21) were married, and indicated that their partner supported and sometimes even managed their medication regime.

The Siegal scale revealed that 8 of the 26 (30.8%) respondents had not taken their medication, once or more, over the last month; the main reason for not taking medication was forgetfulness ($r=1.000$, $p<0.000$). Although the number of respondents is small, there was no significant difference ($r=0.162$, $p<0.43$) in adherence to the mediation regime between the two attitude profiles, 3 of the 12 elderly with the "Satisfied & Easy going" attitude, and 5 of the 14 with the "Reserved & Concerned" attitude. Elderly with both

attitudes tended to forget their medication now and then, but unintentionally. We observed convergent validity between the statement (31); "I sometimes forget my medication" and the Siegal scale with a significant correlation ($r=0.416$, $p<0.034$). There was no significant difference on socio-demographic factors like age or time since transplantation.

Our elderly participants showed little signs of depression; because statements 1, 2 and 5 were generally placed negatively (i.e. they disagreed with these statements). Only 3 of 26 patients agreed with the statement "I think about the death a lot" (statement 2).

Discussion

Prior to this study, little was known how elderly experienced problems with adherence to the post-transplant medication regime. This study revealed two distinct attitudes among elderly transplant recipients: "Satisfied & Easy going" and "Reserved & Concerned". Satisfied and easy-going patients focus on leading a normal and enjoyable life and are not fearful or worried about the consequences of not taking their medication correctly. Reserved and concerned elderly patients experience more psychical and psychological complaints are more fearful of consequences of not taking their medication correctly. Elderly with both attitudes tend to forget their medication now and then, but unintentionally -like found among young transplant recipients (10).

We observed a substantial level of non adherence (30%) in our study population. This is comparable to the findings from a systematic review of the literature that 28% of the adult renal population is non adherent (7). Non adherence is associated with poor clinical outcomes; however death with a functioning graft is still the most common cause of death in the elderly renal transplant population. The two most common causes of death in the elderly are cardiovascular diseases and infection-related mortality after transplantation (46, 48). Although the attitudes towards the post-transplant regime in our study population of elderly patients differed within the sample, a comparable non-adherence score was found for the two groups with distinct attitudes. These results are remarkable because our study population was cognitively well functioning as they were screened for this in the MMSE-test. One consistent determinant of non adherence is social isolation (49). The patients in our study were all living independently and were active in their social network. The risk of non-adherence could be far higher among elderly transplant recipients not enrolled in the present study, those with visual or auditory impairment or moderate to severe cognitive limitations. This indicates that the non-adherence observed here, although considerable, could very well be just the "tip of the iceberg".

The sorting of the cards was feasible for these elderly transplant patients and the post-sort interviews indicated they comprehended the task and the contents. Because the elderly patients had a tendency to be very accurate, the sorting of the cards took a lot of time. In that sense, the post-sort interview also served as a validity check, because any incongruence between the sorting of the cards and explanations of the sort could be remedied. But this was rarely necessary, which is an indication of the validity of the results. The statements and placing them on a score sheet stimulated open communication about the topic. Respondents talked freely and easily about sensitive issues (i.e. death, loneliness), when confronted with these statements. This indicates that the process of sorting a set of opinion statements may also be a helpful instrument in clinical practice to commence and deepen discussions with patients. In doing so they may be able to learn more about how elderly kidney transplant patients experience and deal with their disease, their treatment and their prospects after treatment, and what constitutes these attitudes.

Limitations of the study

Although this sample was sufficient to be able to discover attitude profiles, further research with a larger non selected sample is needed to explore and confirm the relationship with adherence. In particular investigating the attitude profiles and adherence patterns of hard to reach elderly patients who are less independent or have greater co morbidity would be interesting. However this is another argument that the real non-adherence in elderly patients is probably higher than the 30% we observed. In addition, if we want to conduct further studies in this patient population, we should develop methodologies that facilitate participation of vision or hearing impaired patients so we can study the elderly in a broader sense. In this study the Siegal scale was used, which has been criticized for its lack of sensitivity, as self-reporting scales have the tendency to underestimate adherence. Future studies should follow current recommendations in the literature to use multiple measures of adherence (68).

Notwithstanding these limitations, this study offers a unique insight into the attitudes of elderly transplant patients and how these may relate to medication adherence.

References

1. Laupacis A KP, Pus N, Krueger H, Ferguson B, Wong C, Muirhead N. A study of the quality of life and cost-utility of renal transplantation. Kidney Int. 1996;50(1):235-42.
2. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal Transplantation in Elderly Patients Older Than 70 Years of Age: Results From the Scientific Registry of Transplant Recipients. Transplantation. 2007;83(8):1069-74.
3. Heldal K, Leivestad T, Hartmann A, Svendsen MV, Lien BH, Midtvedt K. Kidney transplantation in the elderly--the Norwegian experience. Nephrol Dial Transplant. 2008 March 1, 2008;23(3):1026-31.
4. Huang E, Segev DL, Rabb H. Kidney Transplantation in the Elderly. Seminars in Nephrology. [doi: DOI: 10.1016/j.semnephrol.2009.07.011]. 2009;29(6):621-35.
5. Heldal K, Hartmann A, Grootendorst DC, de Jager DJ, Leivestad T, Foss A, et al. Benefit of kidney transplantation beyond 70 years of age. Nephrol Dial Transplant. 2010 May 1, 2010;25(5):1680-7.
6. Humar A DR, Matas AJ, Najarian JS. Graft and quality of life outcomes in older recipients of a kidney transplant. Exp Clin Transplant. 2003;1(2):69-72.
7. Denhaerynck K, Dobbels F, Cleemput I, Desmyttere A, Schäfer-Keller P, Schaub S, et al. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. Transplant International. 2005;18(10):1121-33.
8. Denhaerynck K, Burkhalter F, Schäfer-Keller P, Steiger J, Bock A, Geest SD. Clinical consequences of non adherence to immunosuppressive medication in kidney transplant patients. Transplant International. 2009;22(4):441-6.
9. Takemoto SK, Pinsky BW, Schnitzler MA, Lentine KL, Willoughby LM, Burroughs TE, et al. A Retrospective Analysis of Immunosuppression Compliance, Dose Reduction and Discontinuation in Kidney Transplant Recipients. American Journal of Transplantation. 2007;7(12):2704-11.
10. Tielen M, van Staa AL, Jedeloo S, van Exel NJA, Weimar W. Q-Methodology to Identify Young Adult Renal Transplant Recipients at Risk for Nonadherence. Transplantation. 2008;85(5):700-6.
11. Cukor D, Rosenthal DS, Jindal RM, Brown CD, Kimmel PL. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. Kidney Int. 2009;75(11):1223-9.
12. Hurd P, Butkovich S. Compliance problems and the older patient: assessing functional limitations. Drug Intell Clin Pharm. 1986;20(3):228-31
13. Cross RM. Exploring attitudes: the case for Q methodology. Health Educ Res. 2005 April 1, 2005;20(2):206-13.
14. Brown S. Q-methodology and qualitative research. Qualitative Health Research. 1996;6(4):561-7.
15. Exel van N, De Graaf G. Q-methodology: A sneak preview2005: Available from: www.qmethod.org or www.rz.unibw-muenchen.de/p41bsmk/qmethod.
16. Dennis KE, Goldberg AP. Weight control self-efficacy types and transitions affect weight-loss outcomes in obese women. Addictive Behaviors. [doi: DOI: 10.1016/0306-4603(95)00042-9].21(1):103-16.
17. Risdon A, Eccleston C, Crombez G, McCracken L. How can we learn to live with pain? A Q-methodological analysis of the diverse understandings of acceptance of chronic pain. Social Science & Medicine. [doi: DOI: 10.1016/S0277-9536(02)00043-6]. 2003;56(2):375-86.
18. Smith. Current systems in psychology: History, theory, research, and applications. Operant subjectivity: Objectivity of subjectivity. Belmont CA: Wadsworth/Thomson Learning; 2001. p. 319-43.

19. Valenta AL WU. Q-methodology. Definition ansd Application in Heatlh Care Informatics. J Am Med Inform Assoc. 1997;4(6):501-10.
20. WHO. WHO, Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization2003.
21. Cukor D, Newville H, Jindal RM. Depression and immunosuppressive medication adherence in kidney transplant patients. General Hospital Psychiatry. 2008;30(4):386-7.
22. Butler JA, Peveler RC, Roderick P, Smith PWF, Horne R, Mason JC. Modifiable risk factors for non-adherence to immunosuppressants in renal transplant recipients: a cross-sectional study. Nephrology Dialysis Tranplantation. 2004;19(12):3144-9.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. [doi: DOI: 10.1016/0022-3956(75)90026-6]. 1975;12(3):189-98.
24. Siegal B. Postrenal transplant compliance: report of 519 responses to a self-report questionnaire. Transplant Proc. 1993;25(4):2502.
25. Schäfer-Keller P, Steiger J, Bock A, Denhaerynck K, Geest SD. Diagnostic Accuracy of Measurement Methods to Assess Non-Adherence to Immunosuppressive Drugs in Kidney Transplant Recipients. American Journal of Transplantation. 2008;8(3):616-26.
26. Dobbels F, Berben L, De Geest S, Drent G, Lennerling A, Whittaker C, et al. The Psychometric Properties and Practicability of Self-Report Instruments to Identify Medication Nonadherence in Adult Transplant Patients: A Systematic Review. Transplantation. 2010;90(2):205-19.

5

The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: A cohort study

Emma K. Massey[1], Mirjam Tielen[1], Mirjam Laging[1], Denise K. Beck[1], Roshni Khemai[1], Teun van Gelder[2], Willem Weimar[1]

[1] Department of Internal Medicine, Nephrology & Tranplantation, Erasmus MC, Rotterdam, The Netherlands
[2] Department of Hospital Pharmacology, Erasmus MC, Rotterdam, The Netherlands

Journal of Psychosomatic Research, 75 (2013) 3; 229-234

Abstract

Objective: Nonadherence to immunosuppressive medication (IM) after kidney transplantation is related to poorer patient and graft outcomes; therefore research into modifiable factors associated with nonadherence is a priority. In this prospective cohort study we investigated whether changes in goal cognitions, illness perceptions, and treatment beliefs were related to self-reported medication adherence six months after kidney transplantation.

Methods: Interviews were conducted with patients in the out-patient clinic six weeks (T1: n = 113) and six months (T2: n = 106) after transplantation. Self-reported adherence was measured using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS© Interview). The Brief Illness Perceptions Questionnaire, Beliefs about Medicines Questionnaire and questions on goal cognitions were also administered at both time points.

Results: Self-reported nonadherence increased significantly between 6 weeks and 6 months after transplantation from 17% to 27%. Importance of medication adherence as a personal goal and self-efficacy to successfully carry out this goal decreased significantly over time. Perceived necessity of immunosuppressive medication was high but significantly decreased over time. Concerns about the medicines were low. There were no significant changes in illness perceptions or concerns over time. An increase in perceived graft longevity (timeline) was related to higher likelihood of nonadherence six months post-transplant. Furthermore, younger adult patients were more likely to be nonadherent six months after transplantation.

Conclusion: The self-reported nonadherence levels found in this study so soon after transplantation demonstrate the need for early and continued intervention after kidney transplantation in order to maximize adherence and consequently clinical outcomes. Changes in (unrealistic) beliefs regarding the longevity of the graft may offer a potential target for intervention among nonadherent patients.

Introduction

Adherence to immunosuppressive medication (IM) is an integral component of self-management after kidney transplantation (KT); however, supporting optimal adherence is often a major challenge for health care professionals [1–3]. Results from a meta-analysis suggested 36 cases per 100 patients per year are nonadherent to IM after KT [4]. Evidence suggests that adherence immediately after KT is often high and gradually declines over time [5], although some authors suggest nonadherence is 'early and pervasive' among kidney transplant patients [6]. Failure to take the correct dose at the correct time is a risk factor for (late) acute rejection, (late) graft failure, and patient mortality [5–8]. Graft failure results in (re)initiation of dialysis and the associated reduction in quality of life. Even small deviations from this strict, lifelong regime can result in poorer outcomes [9]. Nonadherence to as little as 5% of prescribed doses has been associated with significantly higher acute rejection and graft loss [10,11]. For this reason the definition of adherence among this population tends to be strict [12]. Unfortunately, there are many side-effects of IM ranging from excessive hair growth to increased risk of skin cancer. In addition to the clinical consequences, nonadherence is associated with increased health care costs and thus has a negative impact on the cost-effectiveness of renal transplantation [13,14].

Within health psychology, various theoretical models have been developed to explain adherence to health behaviors. Of particular relevance to adherence is Leventhal's Common-Sense Model (CSM). This model describes how cognitive and emotional representations, so-called illness perceptions, are generated in response to a health threat [15]. Illness perceptions consist of perceived causes, consequences, identity (name and symptoms), timeline, emotional response, coherence, and personal and treatment control. Patients generate goals to cope with the health threat and/or associated emotions. Actions are undertaken in order to reduce either the threat itself or the associated emotions. On-going appraisals evaluate response efficacy and feed into subsequent representations in an on-going iterative process. The CSM model has been expanded to incorporate the beliefs that patients hold about their treatment: the perceived necessity for and concerns about the effects of the medication. In the context of kidney transplantation, one of the threats to health is (fear of) graft rejection and adherence to IM can be seen as an action to cope with this threat.

Research among end stage renal disease patients undergoing dialysis has suggested support for a relationship between adherence and illness representations [16,17] and beliefs about medicines [18]. However, to date, few studies have applied the CSM model to adherence after kidney transplantation. In a cross-sectional study among liver, lung and heart transplant recipients in New Zealand, lower treatment control, lower comprehension, greater emotional response, greater experienced symptoms, greater impact on their

lives, lower perceived necessity and greater concerns were related to greater medication nonadherence [19]. Among kidney transplant recipients in the US and UK respectively, greater nonadherence has been related to lower perceived necessity and higher concerns about the medication [20,21]. In contrast, a study on Swedish kidney transplant patients found no relationship between treatment beliefs and adherence [22]. There appears therefore to be a gap in the literature concerning the relationship between adherence and illness perceptions and contradicting evidence regarding treatment beliefs among kidney transplant patients. Furthermore, there is little information on how the medication regime is integrated into and aligned with other personal goals the patient has. Self-regulation theory stipulates that all behavior is goal-directed [23]. Therefore cognitions such as relative importance and self-efficacy for medication taking are likely to offer insights into why this goal-directed behavior is or is not being carried out. For example, behavior is less likely to be consistently carried out if it conflicts with achievement of other personal goals [24]. Finally, studies to date have been cross-sectional resulting in considerable variation in time since transplantation. Given the dynamic character of adherence behavior, prospective measurement is preferable [12].

Therefore the aim of this study was to prospectively investigate the relationships between goal cognitions, illness representations, and treatment beliefs on the one hand and self-reported adherence after kidney transplantation on the other. We formulated the following research question: To what extent are changes in (a) illness perceptions, (b) beliefs about medication (necessity and concerns), and (c) goal cognitions related to self-reported IM adherence? We hypothesized that a decrease in symptoms, emotional response, perceived impact on daily life, goal conflict and an increase in comprehension, perceived personal and treatment control, and self-efficacy would be related to greater adherence. Research into modifiable factors associated with adherence among kidney transplant patients is essential in order to identify potential targets for intervention.

Methods

Participants

Consecutive patients who received a kidney transplant at the Erasmus University Medical Centre, Rotterdam, between 24th August 2010 and 26th October 2011 were invited to participate. In total 212 patients underwent transplantation during this period. Participants were required to meet the following inclusion criteria: over 18 years of age, a functioning graft six weeks post-transplant, sufficient physical and mental ability to be able to participate, and sufficient command of the Dutch language. Forty-four patients did not meet these inclusion criteria and were therefore not approached for participation. Specific reasons for exclusion were: language (n = 23), physical or mental disability (n = 9), graft loss (n = 4),

death (n = 4), primary non-function (n = 3) and emigration (n = 1). Of the remaining 168 patients who were invited to participate, 113 agreed (T1: 67% response rate). Reasons for refusal included fatigue (n = 26), no interest (n = 20), logistical reasons (n = 7), and other (n = 2). Six months after transplantation, 106 patients remained in the study (T2: 94% retention rate) as 2 patients had died, 2 had graft failure, and 3 had health issues or did not wish to participate any longer.

Procedure

Patients who met the inclusion criteria received a Patient Information Form and Informed Consent Form (ICF) during a consultation with the nurse practitioner prior to discharge from the hospital. Patients who signed and returned the ICF were contacted to make an appointment for the interview. Those who did not return the ICF within 2 weeks of discharge were contacted to ascertain whether or not they wished to participate. Interviews at 6 weeks and 6 months after transplantation were conducted by either a nurse practitioner (MT), a psychologist (EM, ML) or a psychology student (RK, DB). The one-to-one interviews (without the presence of family or other caregivers) took approximately 45– 60 min and were combined with the scheduled visit to the outpatient clinic to avoid extra travel, costs or inconvenience. All measures were administered at both time points. The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre (MEC-2010-257) and procedures were in accordance with the Declaration of Helsinki.

Measurements

Medication adherence

Adherence to the IM regime was measured using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS© Interview) [25,26]. Part 1 of this instrument consists of 5 questions on the taking and timing of medication, drug holidays, reduction of the dose and persistence. An affirmative answer to any of the first 3 questions results in assignment to the nonadherent group. This scoring is intentionally strict due to an assumption of underreporting of nonadherence [27]. Part 2 consists of a continuous overall adherence rating scale ranging from 0 (medication never taken as prescribed) to 100 (medication always taken as prescribed). The BAASIS measure was selected as it is short, reliable, valid and sensitive to both timing and taking which is of particular importance for IM after transplantation [26]. A number of studies have demonstrated support for the validity of both parts [28,29]. Specificity and sensitivity of part 2 has been shown to be high [28].

Goal cognitions

Goal cognition items were adapted from the study by Pomaki and colleagues [30]. The extent to which patients endorse IM adherence as an important personal goal was measured using 2 items: 'Taking my medication at the correct time is an important goal for me', and 'Taking the correct dose of my medication is an important goal for me'. The extent to which the patient is committed to taking their medication correctly was measured using 3-items, for example, 'Even if taking my medication correctly is difficult, I will not give up on it'. Conflict with other personal goals was measured using 3 items, for example, 'Taking my medication correctly conflicts with other goals I find important'. The extent to which the patient feels competent in achieving their goal of medication adherence was measured using 3 goal self-efficacy items, for example 'I am capable of taking my medication in the correct way'. Each item was scored on a scale of 1 (totally disagree) to 5 (totally agree). Factor analysis (data not shown) demonstrated a 3 factor structure: importance and commitment (Cronbach's α = .75); self-efficacy (Cronbach's α = .84); and goal conflict (Cronbach's α =.90). Mean scores were calculated per subscale.

Illness perceptions

The Brief Illness Perceptions Questionnaire (B-IPQ) [31] was used to measure the way in which patients perceive their transplant. The 9-item questionnaire measures the cognitive representations of perceived consequences, timeline, personal control, treatment control, comprehensibility, identity, and causes and the emotional representations of concerns and emotional response. The first 8 items are rated on a scale from 0–10. The wording of the items was adapted to fit the context of kidney transplantation. An example is 'How much control do you feel you have over the functioning of your kidney graft'. The final open-ended question measures perceived causes of illness; this was adapted to perceived causes of graft rejection. The B-IPQ has demonstrated good test–retest reliability and concurrent validity among renal patients and other patient groups [31].

Beliefs about medication

The Beliefs about Medicines Questionnaire [32] was used to measure perceived necessity of and concerns specifically about IM. An example of an item on the necessity subscale is 'Without my medicines I would become very ill'. An example of an item on the concerns subscale is 'I sometimes worry about the long-term effects of my medicines'. Each item was rated on a 5-point scale ranging from 1 (totally disagree) to 5 (totally agree). Each 5-item subscale was summed resulting in a score ranging from 5 to 25. Satisfactory reliability and validity have previously been demonstrated [32]. A necessity–concerns differential can also be calculated by subtracting the concerns subscale from the necessity subscale [18]. This demonstrates a cost–benefit analysis where-by a positive value indicates that the perceived

benefits outweigh the costs.

Sociodemographic and medical characteristics

The following characteristics were recorded and dichotomized for use in the analyses: gender (M/F), employment (paid work versus no paid work), ethnicity (Dutch versus non-Dutch), marital status (married/living together versus single/widowed/divorced), type of donor (living versus deceased), pre-emptive transplantation (yes/no) and number of transplants (0 = 1; 1 ≥ 1). Education was categorized into low, middle and high. Age was recorded as a continuous variable.

Statistical analysis

Perceived causes of kidney rejection (B-IPQ) were coded independently by two raters (EM and DB). After the initial rating, items with differing categorization were discussed and the coding was refined. Measurement of agreement was tested using Cohen's kappa. For univariate analyses, chi-squared and independent samples t-tests were conducted to assess differences between independent groups for nominal and continuous variables respectively. When data were not normally distributed the Mann–Whitney test was conducted. Paired t-tests were used to test change over time in related samples. Pearson's correlation or Spearman's rho (for non-normal data) were used to test for associations between continuous variables. The McNemar test for related dichotomous variables was used to assess changes in adherence classification. For multivariate analyses, binomial logistic regression analyses were conducted to assess the extent to which change in psychological variables (delta scores) was related to adherence/nonadherence controlling for sociodemographic variables. Delta scores were used in order to take into account the prospective nature of the data. The model was built in blocks: (1) socio-demographic and medical variables; (2) psychological variables. A stepwise backward elimination process of non-significant variables was employed to generate the most parsimonious model. Independent variables with a p-value less than .10 were entered into the model. Only significant variables ($p < .05$) are presented in the final model. Analyses were carried out using the Statistical Package for Social Sciences, version 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Descriptive and univariate analyses

Sociodemographic characteristics

Sociodemographic characteristics of the 113 participants at T1 are presented in Table 1.

Table 1 Demographic characteristics of participants at baseline (N=113)

Variable	*Total*	*Adherent group (n=94)*	*Nonadherent group (n=19)*
Age: median (range)	53 (19-75)	52.5 (19-75)	57.0 (22-72)
Gender: % men (n)	64.6 (73)	66.0 (62)	57.9 (11)
Marital status: % (n)			
Single/divorced/widowed	26.5 (30)	24.5 (23)	36.8 (7)
Married/living together	73.5 (83)	75.5 (71)	63.2 (12)
Ethnicity: % (n)			
Dutch	84.1 (95)	84.0 (79)	84.2 (16)
Non-Dutch	15.9 (18)	16.0 (15)	15.8 (3)
Employment: % (n)			
Paid employment (full/part-time)	45.2 (51)	41.5 (39)	63.2 (12)
Not in paid employment	54.9 (62)	58.5 (55)	36.8(7)
Education: % (n)			
Low	23.9 (27)	23.4 (22)	26.3 (5)
Middle	56.6 (64)	55.3 (52)	63.2 (12)
High	19.5 (22)	21.3 (20)	10.5 (2)
Donor type: % (n)			
Living	78.8 (89)	77.7 (73)	84.2 (16)
Deceased	21.2 (24)	22.3 (21)	15.8 (3)
Relationship of the living donor to the patient: % (n)[a]			
Partner	17.7 (20)	19.1 (18)	10.5 (2)
Parent	13.3 (15)	13.8 (13)	10.5 (2)
Child	8.8 (10)	8.5 (8)	10.5 (2)
Sibling	9.7 (11)	9.6 (9)	10.5 (2)
Aunt/uncle/cousin	1.8 (2)	2.2 (2)	0.0
Family-in-law	1.8 (2	2.1 (2)	0.0
Non-family	7.1 (8)	7.4 (7)	5.3 (1)
National Kidney Exchange	14.2 (16)	10.6 (10)	31.6 (6)
Anonymous	6.2 (7)	6.4 (6)	5.3 (1)
Pre-emptive transplantation: % (n)	36.3 (41)	34.0 (32)	47.4 (9)
Number of transplants: median (range)	1 (1-5)	1 (1-2)	1 (1-5)
Duration hospital admission: median (range)	13 (8-59)	13 (9-59)	12 (8-41)

[a]22 missing

Eighty-one percent (n = 91) had undergone a primary kidney transplant where as 22 patients had undergone re-transplantation. Three patients had previously undergone another type of transplant (2 liver, 1 lung). The large majority of 87% (n = 98) reported co-morbidity (such as high blood pressure, diabetes, cardiovascular problems, cerebrovascular accident). There were no significant differences in sociodemographic characteristics of responders and non-responders (data not shown).

Adherence

Adherence classification (BAASIS Part 1). Table 2 shows adherence at T1 and T2. Six weeks after transplantation 17% (n = 19) were nonadherent. Six months after transplantation, this increased to 27% (n = 29). Nonadherence was greatest for the timing dimension. At both time points there were very few or no individuals who skipped more than two doses in a row, altered the dose themselves or stopped taking the medication altogether.

Table 2 Adherence at six weeks (T1) and six months (T2) after transplantation

	T1 (n=113) n (%)	T2 (n=106) n (%)
BAASIS part 1 1a. Taking dimension: Do you remember missing a dose of your IM in the past 4 weeks?	9 (8.0)	13 (12.3)
Once	8 (7.1)	12 (11.3)
Twice	1 (0.9)	1 (0.9)
1b. Drug holidays: Do you remember having skipped two or more doses of your IM in a row in the past 4 weeks?	0	0
2. Timing dimension: Do you remember having taken your IM more than 2 h before or after the prescribed dosing time in the past 4 weeks?	12 (10.6)	20 (18.9)
Once	10 (8.8)	14 (13.2)
2-3 times	1(0.9)	2 (1.8
4-5 times	1 (0.9)	3 (2.8)
Every 2 to 3 days	0	0
Almost daily	0	1 (0.9)
3. Reduction of dose: Have you altered the prescribed amount of your IM during the past 4 weeks without your doctor telling you to do so?	0	1 (0.9)
4. Persistence: Have you stopped taking your IM completely in the past 4 weeks without your doctor telling you to do so?	0	0
Categorised as nonadherent	19 (16.8)	29 (27.4)
BAASIS part 2 5. Overall adherence rating median (range; interquartile range)	100 (77-100;5)	99 (50-100;10)

With regard to changes in BAASIS classification over time, 68 patients were classified adherent at both T1 and T2; 9 patients changed from being nonadherent at T1 to adherent at T2; 22 patients changed from being adherent at T1 to nonadherent at T2; and 7 patients were nonadherent at both time points. Therefore, in total 38 (34%) patients were nonadherent at some point in the study. The McNemar test showed that significantly more patients became nonadherent over time ($\chi^2 = 4.65$, $p < .05$).

At T1 and T2 there were no significant differences between the adherent and nonadherent groups on gender, ethnicity, marital status, education level, employment, type of donor,

or pre-emptive transplantation. No difference was found in age between the adherent and nonadherent groups at T1. At T2 those categorised as nonadherent were significantly younger (M = 44.72, SD = 13.33) than those categorised as adherent (M = 53.13, SD = 12.70), t(104) = 2.99, p < .01. At T1 there was no difference between adherent and nonadherent groups according to number of kidney transplants. At T2 those categorised as nonadherent were more likely to have undergone re-transplantation, $\chi^2 = 7.16$, p < .01.

Overall adherence scale (BAASIS Part 2). Table 2 shows that the median overall adherence rating is generally high but significantly decreases over time (z = −3.18, p < .001). The Wilcoxon signed-rank test showed that 36 patients had a negative ranking (T2 adherence lower than T1), 20 patients had a positive ranking (T2 adherence higher than T1) and 50 patients had a tied ranking (same ranking at T1 and T2). Overall adherence rating at T1 was significantly positively correlated with age (Spearman's rho = .21, p < .05): younger participants rated themselves as less adherent. Also at both T1 and T2 patients who were undergoing their first transplant reported higher overall adherence, p < .05. No other associations with sociodemographic or medical characteristics were found.

Personal goal cognitions

The mean scores presented in Table 3 show that medication taking is an important personal goal, patients feel capable of achieving this goal and report low goal conflict.

Table 3 Paired t-tests for changes in goal cognitions, illness perceptions and treatment beliefs

	T1 Mean (SD)	T2 Mean (SD)	z
Goal cognitions [a]			
Goal importance	4.62 (0.45)	4.52 (0.49)	-2.10*
Goal conflict	1.44 (0.72)	1.55 (0.71)	-1.77
Goal self-efficacy	4.74 (0.45)	4.63 (0.60)	-2.05*
	T1 Mean (SD)	T2 Mean (SD)	t
Beliefs about medicines			
Necessity	22.77 (2.5)	22.02 (3.0)	2.46*
Concerns	10.47 (4.1)	11.08 (3.8)	-1.80
N-C Differential [b]	12.30 (4.9)	10.94 (5.0)	2.97**
Illness perceptions			
Consequences	7.64 (2.6)	7.29 (2.6)	1.37
Timeline	8.00 (1.8)	8.21 (1.8)	-0.99
Personal control	7.64 (2.0)	7.81 (1.6)	-0.75
Treatment control	8.99 (1.1)	9.00 (1.1)	-0.08
Identity	2.69 (2.4)	2.93 (2.4)	-0.98
Concerns	5.72 (2.9)	5.74 (3.1)	-0.06
Coherence	7.39 (2.4)	7.61 (2.3)	-0.94
Emotional response	3.89 (3.1)	3.47 (2.8)	1.47

[a] Due to non-normally distributed delta's, Wilcoxon signed-rank tests were conducted.
[b] N-C differential = necessity-concerns differential.
* $p < .05$; ** $p < .01$.

Table 3 also shows that on average, importance of adherence to medication as a personal goal and self-efficacy to achieve that goal, significantly decreased over time. Greater goal importance was positively correlated with overall adherence rating (T1: rho = .31, $p < .001$; T2: rho = .47, $p < .001$). Self-efficacy at T2 also correlated with overall adherence (rho = .30, $p < .01$). Goal conflict did not significantly correlate with overall adherence. There were no significant differences in goal cognitions between the adherent and nonadherent groups at T1 and T2.

Beliefs about medicines

Patients reported high perceived necessity of IM and relatively lower concerns as indicated by the positive necessity–concerns differential (see Table 3). Perceived necessity of the IM to maintain the current health status significantly decreased over time. This translated into a significant decrease in the necessity–concerns differential. We note that the value of the necessity–concerns differential remains positive indicating that the perceived benefits outweigh the costs at both T1 and T2. There were no significant differences in beliefs about medicines between the adherent and nonadherent groups at both time measurements (data not shown).

Illness perceptions

At T1, timeline (rho = .22, $p < .05$) was positively correlated with overall adherence rating; patients who think that their graft will last longer reported higher overall adherence. There was a trend for greater adherence to be related to greater personal control (rho = .18, $p = .06$) and emotional response (rho = .18, $p = .06$). At T2, greater perceived treatment control was related to higher overall adherence (rho = .24, $p < .05$). These correlations were significant but nevertheless weak. There were no associations between change in illness perceptions and change in overall adherence rating ($r = -.14–.08$, $p > .05$). There were no significant differences in illness perceptions between the adherent and nonadherent groups at T1 (data not shown). At T2, the consequences scale (impact of transplantation on life) was rated as significantly higher by the nonadherent group ($M = 8.03$, $SD = 1.82$) than the adherent group ($M = 7.01$, $SD = 2.78$), $t(78) = -2.2$, $p < .05$. Illness perceptions did not significantly change between T1 and T2 (see Table 3).

On the final question of the IPQ, participants were requested to report 3 possible causes of allograft rejection. Inter-rater agreement was high for the categorisation of these causes at T1 (Cohen's kappa = .95–.97) and T2 (Cohen's kappa = .95–.96). Nonadherence to IM was reported as a cause of allograft rejection by 83% of patients at both time points, however, the remaining patients failed to report nonadherence as a potential cause of allograft rejection. There was no significant relationship between naming IM nonadherence as a cause of rejection and adherence categorisation or overall adherence rating at T1 or

T2. Other commonly reported causes of graft rejection were unhealthy lifestyle (T1 37%; T2 36%), poor nutrition and fluid maintenance (T1 34%; T2 25%), and bacteria, infection or illness (T1 19%; T2 14%). Causes that were reported less frequently (<10%) were bad luck/uncontrollable factors, immune response, smoking, poor graft match/compatibility, natural deterioration of graft functioning over time, inadequate contact with health care professionals, stress, poor fitness, weight, and alcohol or drug use. A small minority (T1 6%; T2 3%) could not name any causes of allograft rejection.

Multivariate analyses

Logistic regression was carried out to investigate the association between changes in cognitions over time and adherence classification at T2. Table 4 shows the final model in which only variables with a significant association are presented. This final model correctly classifies 74.5% of patients. When controlling for adherence at T1, an increase in the perceived longevity of the graft was related to 1.32 greater odds of nonadherence at T2. Conversely, greater age was related to lower odds of nonadherence at T2. Results were the same when using timing and taking dimensions separately (data not shown).

Table 4 Logistical regression with adherence classification six month after transplantation as the dependent variable

				95% CI for Exp(B)	
	B (SE)	Wald	Exp(B)	Lower	Upper
Constant	2.27 (1.06)	4.62	9.71		
Adherence Classification T1	-0.94 (0.62)	2.30	0.39	0.13	1.32
Age	-0.05 (0.02)**	8.97	0.95	0.92	0.98
IPQ2 Timeline Δ	0.27 (0.13)*	4.64	1.32	1.03	1.69

Note: R^2 = .21 (Nagelkerke). Model χ^2 (3) = 16.20, p < .001. * p < .05; ** p < .01.

Linear regression was also conducted to investigate the association between changes in cognitions over time and self-reported overall adherence rating at T2. However, when controlling for overall adherence rating at T1, none of the change variables were significantly.

Discussion

This study adds new insights into changes in adherence and the relationship with changing cognitions over time. Clinically speaking, a nonadherence rate of 17% as early as six weeks after transplantation is cause for concern. Nonadherence as early as the first weeks after discharge has also previously been reported [6]. Moreover, this rate increased to 27% six

months after transplantation. Previous studies have shown that declining adherence over time is related to higher risk of poorer clinical outcomes [10,11]. There is thus a clear need for early intervention and research into modifiable factors that are related to nonadherence.

In line with previous literature [7,20,33], younger patients in this study were more likely to be nonadherent six months after transplantation. Nonadherence has typically been demonstrated to be an issue among adolescent patients, however since our participants were all over the age of 18, this finding highlights the need for continued attention to medication adherence beyond adolescence and into young adulthood. Therefore, within adult nephrology services, young adults form a risk group for nonadherence and interventions should be tailored to this group. Furthermore, patients who showed an increase in perceived allograft longevity were more likely to be nonadherent six months after transplantation. Opposite effects of timeline have been found among dialysis patients whereby the perceived temporary nature of their illness was related to lower adherence [16,17]. This demonstrates the context and treatment specificity of beliefs and the importance of investigating these specific beliefs in each patient population. We speculate that after transplantation an increasing, unrealistic belief regarding the expected graft survival may undermine medication taking. Unrealistic beliefs regarding longevity of the graft could offer a potential target for intervention aimed at maintaining adherence over time. In the clinic, nephrologists should be vigilant to correct beliefs that the graft will last an entire lifetime, particularly among younger patients.

One issue that may have affected our results is that of underreporting leading to nonadherent participants assigned to the adherent group. In order to take this into account we employed the BAASIS interview, which was developed to take underreporting into consideration. Given that even small deviations in the regime are linked to poorer outcomes [9] this strict approach to defining adherence in this population appears justified. Part of our approach was also to measure self-reported adherence using a personal, confidential interview as advocated by Butler and colleagues [34], although social desirability is difficult to avoid in a clinical environment. Another issue may be that of inadequate power to find differences between the adherent and nonadherent groups, given the lower number of nonadherent patients for statistical analyses.

Despite the high level of self-reported nonadherence, we also found high levels of motivation for medication adherence and perceived ability to carry out this behavior successfully. Furthermore, the level of conflict with other personal goals was low. Therefore, other factors must play a role in nonadherence in this early stage. These baseline cognitions appear to be adaptive as we know from previous research that self-efficacy relates to better self-management including medication adherence [35]. Similarly in this study, in the univariate analyses, greater goal importance was related to greater self-reported overall adherence. However, these cognitions changed over time: the importance of medication

adherence as a personal goal and perceived ability to carry out this behavior successfully (self-efficacy) significantly decreased over time. In the first six months post-transplant there was no evidence for a relationship between changing goal cognitions and adherence classification. The question remains as to how these cognitions will develop longer after transplantation. One study among haemodialysis patients has shown the potential impact of a goal-based intervention on adherence [36] however this is yet to be translated to the post-transplant period. Given the high baseline level of motivation and self-efficacy, strategies such as motivational interviewing may prove useful tools for interventions that aim to promote maintenance of motivation for medication adherence over time.

In general, transplantation was reported to have a large impact on the patient's lives (consequences). Patients perceived high control over the functioning of the graft and even higher treatment control. Self-reported complaints from the transplant were relatively low. In comparison to illness perceptions and treatment beliefs among lung, heart and liver transplant recipients [19], kidney transplant patients reported on average greater perceived necessity of the medication and lower concerns about the effects of the medication, but also greater consequences of transplant on their lives, greater concerns about the transplant and lower coherence [Broadbent 2012, personal communication]. In this study we did not find differences between adherent and nonadherent groups on illness perceptions and beliefs about medicines whereas Kung and colleagues did [19]. It is possible that the difference between findings is related to time since transplantation as previous studies were cross-sectional and thus included patients with varying time (often years) since transplantation. Early post-transplant patients are still recovering from surgery, rehabilitating, and establishing new self-management routines. Therefore, some beliefs may be more pertinent to adherence immediately after transplantation while others may become pertinent later after transplantation. For example, an increase in timeline was related to greater self-reported nonadherence in the early post-transplant period in our study whereas lower treatment control and higher symptom distress were related to nonadherence among patients years post-transplant in the study by Kung and colleagues. Illness perceptions and beliefs are dynamic in nature: perceptions are shaped by experiences and appraisal of coping efforts, these appraisals in turn influence subsequent actions in an on-going iterative process. It is therefore important to investigate how perceptions change over time in order to gain insights into these dynamic processes and how changes may influence adherence behavior.

Conflict of interest

The authors have no conflicting interests to report.

Acknowledgments

This study was supported by an internal Erasmus MC grant 'Evidence Based Care by Nurses'.

References

[1] Ruppar TM. Medication adherence research: more theory-driven interventions are needed. West J Nurs Res 2010;32:847–8.

[2] DiMatteo MRP. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 2004;42:200–9.

[3] Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. Patient Educ Couns 2002;48:177–87.

[4] Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. Transplantation 2007;83:858–73.

[5] Loghman-Adham L. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. Am J Manag Care 2003;9:155–71.

[6] Nevins TE, Matas AJ. Medication noncompliance: another iceberg's tip. Transplantation 2004;77:776–8.

[7] Denhaerynck K, Dobbels F, Cleemput I, Desmyttere A, Schäfer-Keller P, Schaub S, et al. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. Transpl Int 2005;18:1121–33.

[8] Vlaminck H, Maes B, Evers G, Verbeke G, Lerut E, Van Damme B, et al. Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. Am J Transplant 2004;4:1509–13.

[9] De Geest S, Abraham I, Moons P, Vandeputte M, van Cleemput J, Evers G, et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J Heart Lung Transplant 1998;17:854–63.

[10] Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int 2001;60:1565–70.

[11] Nevins TE, Thomas W. Quantitative patterns of azathioprine adherence after renal transplantation. Transplantation 2009;87:711–8.

[12] De Geest S, Denhaerynck K, Dobbels F. Clinical and economic consequences of non-adherence to immunosuppressive drugs. In: Grinyó J, editor. International Transplantation Updates. Barcelona, Spain: Permanyer Publications; 2011.

[13] Cleemput I, Kesteloot K, Vanrenterghem Y, Sabina De G. The economic implications of non-adherence after renal transplantation. Pharmacoeconomics 2004;22:1217–34.

[14] Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. Am J Transplant 2009;9:2597–606.

[15] Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In: Cameron LD, Leventhal H, editors. The self-regulation of health and illness behaviour. London: Routledge; 2003. p. 42–65.

[16] Chilcot J, Wellsted D, Farrington K. Illness representations are associated with fluid nonadherence among hemodialysis patients. J Psychosom Res 2010;68:203–12.

[17] O'Connor SM, Jardine AG, Millar K. The prediction of self-care behaviors in end-stage renal disease patients using Leventhal's Self-Regulatory Model. J Psychosom Res 2008;65:191–200.

[18] Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 1999;47:555–67.

[19] Kung M, Koschwanez HE, Painter L, Honeyman V, Broadbent E. Immunosuppressant nonadherence in heart, liver, and lung transplant patients: associations with medi- cation beliefs and illness perceptions. Transplantation 2012;93:958–63.

[20] Chisholm-Burns M, Pinsky B, Parker G, Johnson P, Arcona S, Buzinec P, et al. Factors related to immunosuppressant medication adherence in renal transplant recipients. Clin Transplant 2012;26:706–13.

[21] Butler JA, Peveler RC, Roderick P, Smith PWF, Horne R, Mason JC. Modifiable risk factors for non-adherence to immunosuppressants in renal transplant recipients: a cross-sectional study. Nephrol Dial Transplant 2004;19:3144–9.

[22] Lennerling A, Forsberg A. Self-reported non-adherence and beliefs about medication in a Swedish kidney transplant population. Open Nurs J 2012;6:41–6.

[23] Austin JT, Vancouver JB. Goal constructs in psychology: structure, process, and content. Psychol Bull 1996;120:338–75.

[24] Boersma SN, Maes S, Joekes K, Dusseldorp E. Goal processes in relation to goal attainment: predicting health-related quality of life in myocardial infarction patients. J Health Psychol Dec 2006;11:927–41.

[25] Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients: an overview of instruments developed to date. Pharmacoeconomics 2007;25:269–86.

[26] Dobbels F, Berben L, De Geest S, Drent G, Lennerling A, Whittaker C, et al. The psycho- metric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review. Transplantation 2010;90:205–19.

[27] Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999;21:1074–90.

[28] Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treat- ment outcome. AIDS 2002;16:269–77.

[29] Glass TR, De Geest S, Weber R, Vernazza PL, Rickenbach M, Furrer H, et al. Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study. J Acquir Immune Defic Syndr 2006;41:385–92.

[30] Pomaki G, Maes S, ter Doest L. Work conditions and employees' self-set goals: goal pro- cesses enhance prediction of psychological distress and well-being. 2004;30:685–94.

[31] Broadbent E, Petrie KJ, Main J, Weinman J. The Brief Illness Perception Questionnaire. J Psychosom Res 2006;60:631–7.

[32] Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the de- velopment and evaluation of a new method for assessing the cognitive representa- tion of medication. Psychol Health 1999;14:1–24.

[33] Dobbels F, Ruppar T, De Geest S, Decorte A, Van Damme-Lombaerts R, Fine RN. Ad- herence to the immunosuppressive regimen in pediatric kidney transplant recipi- ents: a systematic review. Pediatr Transplant 2010;14:603–13.

[34] Butler JA, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. Transplantation 2004;77:786–9.

[35] Curtin RB, Walters BAJ, Schatell D, Pennell P, Wise M, Klicko K. Self-efficacy and self-management behaviors in patients with chronic kidney disease. Adv Chronic Kidney Dis 2008;15:191–205.

[36] Christensen AJ, Moran PJ, Wiebe JS, Ehlers SL, Lawton WJ. Effect of a behavioral self-regulation intervention on patient adherence in hemodialysis. Health Psychol 2002;21:393–7.

6

Discrepancies Between Beliefs and Behavior: A Prospective Study Into Immunosuppressive Medication Adherence After Kidney Transplantation

Emma K. Massey[1], Mirjam Tielen[1], Mirjam Laging[1], Reinier Timman[2], Denise K. Beck[1], Roshni Khemai[1], Teun van Gelder[3], and Willem Weimar[1]

[1] Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.
[2] Department of Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands.
[3] Departments of Internal Medicine and Hospital Pharmacology, Erasmus Medical Center, Rotterdam, The Netherlands.

Transplantation 2015; 99 (2): 375-380

Abstract

Background: Nonadherence to immunosuppressive medication after kidney transplantation is a behavioral issue and as such it is important to understand the psychological factors that influence this behavior. The aim of this study was to investigate the extent to which goal cognitions, illness perceptions, and treatment beliefs were related to changes in self-reported immunosuppressive medication adherence up to 18 months after transplantation.

Methods: Interviews were conducted with patients in the outpatient clinic 6 weeks (T1; n = 113), 6 months (T2; n = 106), and 18 months (T3; n = 84) after transplantation. Self-reported adherence was measured using the Basel Assessment of Adherence to Immunosuppressive Medications Scale Interview. Psychological concepts were measured using the Brief Illness Perceptions Questionnaire, Beliefs about Medicines Questionnaire, and questions on the importance of adherence as a personal goal, conflict with other goals, and self-efficacy for goal attainment.

Results: Nonadherence significantly increased over time to 31% at T3. Perceived necessity of medication, perceived impact of transplant on life (consequences) and emotional response to transplantation significantly decreased over time. Participants who reported low importance of medication adherence as a personal goal were more likely to become nonadherent over time.

Conclusions: Illness perceptions can be described as functional and supportive of adherence, which is inconsistent with the pervasive and increasing nonadherence observed. There appears therefore to be a discrepancy between beliefs about adherence and actual behavior. Promoting (intrinsic) motivation for adherence goals and exploring the relative importance in comparison to other personal goals is a potential target for interventions.

Introduction

Immunosuppressive medication is a lifelong requirement after organ transplantation and an important component of self-management. Numerous studies have demonstrated early and pervasive immunosuppressive medication nonadherence (IMNA) after transplantation.(1-6) Recipients of a kidney, in comparison to recipients of other organs, demonstrate the highest level of IMNA,(6) which in turn is related to poorer clinical outcomes.(3,7) Despite the established prevalence of IMNA, there are few studies that investigate potential modifiable targets for intervention to promote adherence among transplant patients. Improving adherence is a key target in improving long-term transplant outcomes.(8)

In the area of health psychology, the common sense model of self-regulation has often been applied to the study of adherence behavior. The theory posits that individuals develop illness and treatment representations in an attempt to make sense of and guide management of the illness.(9–11) Illness perceptions include the perceived cause(s) of the illness, the label it is given (identity), timeline (chronic, acute, or cyclical), personal control over outcomes, the effectiveness of treatment to control outcomes, understanding of the illness, and concerns about, and emotional reaction to the illness. Treatment beliefs include the perceived necessity of treatment to maintain the current health state and concerns about the treatment. These perceptions inform goals set and actions undertaken to cope with the illness, such as medication taking. To understand transplant patients and their health behaviors, it is important to understand how they perceive their illness and medication as well as how this medication regime fits into, or conflicts with, the person's goals in life.

Research among diabetes(12) and dialysis patients has suggested support for a relationship between medication adherence and illness and treatment perceptions.(11,13,14) Among solid organ transplant recipients, evidence is mixed. Some studies demonstrated a relationship between perceptions and adherence(4,15–17) while one did not.(18) One major limitation of these studies is the cross-sectional design, which precludes investigation of changes over time and causal relationships.

In this study, we add to the literature by contributing a prospective study on the extent to which illness and treatment perceptions and goal cognitions predict adherence up to 18 months after transplantation. Analyses on the data from the first 2 timepoints revealed that patients were highly motivated to take their medication, felt efficacious in doing so, and understood the necessity for the medication to maintain current health state. However, goal importance, self-efficacy to achieve this goal and perceived necessity for the medication decreased significantly over time. Lower age and an increase in perceived longevity of the graft were related to nonadherence at 6 months.(19) For this analysis on all 3 timepoints up to 18 months, we formulated the following research questions: (1) Does adherence level change over time? (2) Do illness and treatment perceptions change over time? (3) Do perceptions predict IMNA in the first 18 months after transplantation?

Materials and methods

Participants

Consecutive patients who received a kidney transplant at the Erasmus University Medical Centre, Rotterdam, between August 24, 2010, and October 26, 2011, were invited to participate. Inclusion criteria were as follows: older than 18 years, sufficient physical and mental ability to participate, and sufficient command of the Dutch language.

Procedure

Patients who met the inclusion criteria received a Patient Information Form and Informed Consent Form during a consultation with the nurse practitioner before discharge from the hospital. Patients who returned the signed consent form were contacted to make an appointment; however, those who experienced graft failure by week 6 after transplantation were excluded. Interviews were conducted individually and were combined with the scheduled visit to the outpatient clinic to maximize participation. Interviews at T1, T2, and T3 were conducted by a nurse practitioner (M.T.), a psychologist (E.M., M.L.), or psychology student (R.K., D.B.). During the face-to-face interview, the questionnaires used in this study were administered. The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre (MEC-2010-257).

Measurements

Medication Adherence

Adherence to the immunosuppressive medication regime was measured using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS Interview),(20) which consists of 4 questions on the taking and timing of medication, drug holidays, reduction of the dose, and persistence. We chose the BAASIS to measure medication (non) adherence because it was specifically developed for immunosuppressive medications and consequently takes into consideration timing as well as taking. An affirmative answer to any of the first 4 items results in assignment to the nonadherent group. This scoring is intentionally strict due to an assumption of under-reporting of nonadherence.(21) The BAASIS measure is a brief, reliable, and valid instrument.(22,23)

Goal Cognitions

Goal cognition items were adapted from earlier measures of goal cognitions.(24,25) The extent to which patients endorse immunosuppressive medication adherence as an important personal goal was measured using 2 items, for example, “Taking my medication at the correct time is an important goal for me.” Goal commitment was measured using 3 items, for example, “Even if taking my medication correctly is difficult, I will not give up on

it." Conflict with other personal goals was measured using 3 items, for example, "Taking my medication correctly conflicts with other goals I find important." Confidence in achieving their medication goal was measured using 3 goal self-efficacy items, for example, "I am capable of taking my medication in the correct way." Each item was scored on a scale of 1 (totally disagree) to 5 (totally agree). Principle components analysis on the baseline data (not shown) demonstrated a 3-factor structure: importance and commitment (Cronbach α = 0.75), self-efficacy (Cronbach α = 0.84), and conflict (Cronbach α = 0.90). Mean scores were calculated per subscale (range 1–5).

Illness Perceptions

The Brief Illness Perceptions Questionnaire,(26) a widely implemented questionnaire to measure illness perceptions, was adapted to measure the way in which patients perceive their transplant. The first 8 items used here measure the perceived consequences, timeline, personal control, treatment control, comprehensibility, identity (symptoms), concerns (about rejection), and emotional response. Items were rated on a scale from 0 to 10. The Brief Illness Perception Questionnaire is brief and has demonstrated good test-retest reliability and concurrent validity among (renal) patients.(26)

Beliefs About Medication

The Beliefs about Medicines Questionnaire(27) was used to measure perceived necessity of, and concerns specifically about, immunosuppressive medication. Each item was rated on a 5-point scale ranging from 1 (totally disagree) to 5 (totally agree). Each 5-item subscale was summed resulting in a score ranging from 5 to 25. Horne and colleagues(27) demonstrated satisfactory reliability and validity.

Sociodemographic and Medical Characteristics

The following characteristics were recorded and dichotomized for use in the analyses: sex (male/female), employment (paid work versus no paid work), ethnicity (Dutch versus non-Dutch), marital status (married/living together versus single/widowed/divorced), type of donor (living versus deceased), preemptive transplantation (yes/no), number of transplants (1/>1), and comorbidity (yes/no). Education was categorized into low, middle, and high. Age and duration of hospital admittance were recorded as a continuous variable.

Time

For purpose of analysis and to accurately represent the length of time between measurements, timepoints were coded 0 at baseline (T1), 1 at 6 months follow-up (T2), and 3 at 18 months follow-up (T3).

Statistical Analysis

To answer the first 2 research questions, multilevel logistic and linear regression analyses were conducted on adherence and psychological variables, respectively, with time and the quadratic function of time as the predictors. To answer the third research question, multilevel logistic regression analyses were conducted to assess the contribution of psychological factors and time and the interactions of these factors to adherence categorization. Multilevel logistic regression corrects for bias when absence of data is dependent on characteristics that are present in the models (missing at random).(28) Time was entered into the analyses to investigate the linear effects of time on outcomes. A significant linear effect implies an increase or decrease in the outcome over time. Additionally, the quadratic function of time was entered as a predictor to investigate the nonlinear effects of time (eg, a U-shaped regression line). Level 1 data was time and level 2 was participants. All predictors were entered into the model, and backward elimination was used to exclude nonsignificant predictors. Only significant models are presented. Analyses were carried out using the Statistical Package for Social Sciences, version 21 (IBM Corporation, Armonk, NY).

Results

Participant Characteristics

During the inclusion period, 212 patients underwent transplantation, of which 44 (21%) did not satisfy the inclusion criteria. Of the remaining 168 patients, 113 participated at T1 (67% response rate). Reasons for refusal included fatigue (n = 26), no interest (n = 20), logistical reasons (n = 7), and other (n = 2). At T2, 106 patients participated (94% retention). At T3, 84 patients participated (74% retention). Of the 29 dropouts, 4 patients died, 4 patients had graft failure, and 21 had health issues or did not wish to participate further.

Sociodemographic and medical characteristics of participants are presented in Table 1. The majority (87%) reported comorbidity, such as diabetes and cardiovascular problems. There were no significant differences in sociodemographic or medical characteristics of responders and nonresponders.(29)

Table 1. Baseline socio-demographic and medical characteristics

Characteristic	Total group (N=113)
Age: median (range)	53 (19-75)
Gender: % men (n)	64.6 (73)
Marital status: % (n)	
Single / Divorced / Widowed	26.5 (30)
Married / living together	73.5 (83)
Ethnicity: % (n)	
Dutch	84.1 (95)
Non-Dutch	15.9 (18)
Employment: % (n)	
Paid employment (full/part-time)	45.2 (51)
Not in paid employment	54.9 (62)
Education: % (n) [a]	
Low	12.4 (14)
Middle	63.7 (72)
High	21.2 (24)
Donor type: % (n)	
Living	79.6 (90)
Deceased	20.4 (23)
Pre-emptive transplantation: % (n)	36.3 (41)
Number of transplants: median (range)	1 (1-5)
Duration of hospital admission: median (range)	13 (8-59)

[a] 3 missing

Change in Adherence

The number of participants categorized as nonadherent significantly increased from 17% (19/113) at T1 to 27% (29/106) at T2 to 31% (26/84) at T3. Multilevel logistic regression showed that time was a significant predictor of nonadherence: B = 0.045; 95% CI, 0.007-0.082, Wald $\chi 2$ (1) = 5.313; P = 0.021.

Change in Psychological Factors

Mean scores of psychological factors at each timepoint are presented in Table 2. Multilevel linear regression demonstrated significant linear (P = 0.008) and quadratic (P = 0.009) effects of time on necessity for medication. Perceived necessity of immunosuppressive medication decreased in the first 6 months and subsequently increased at 18 months. Perceived consequences (p = .016) and emotional response (p = .033) significantly decreased over time. Table S1 (SDC, http://links.lww.com/TP/B117) presents the full multilevel model for each psychological variable.

Table 2. Means and standard deviations per timepoint for illness perceptions, treatment beliefs and goal cognitions.

	T0 (n=113) Mean (SD)	T1 (n=106) Mean (SD)	T2 (n=84) Mean (SD)	Significant linear effect of time	Significant quadratic effect of time
Goal cognitions					
Goal importance	4.62 (0.46)	4.52 (0.50)	4.53 (0.46)		
Goal conflict	1.44 (0.72)	1.55 (0.71)	1.58 (0.82)		
Goal self-efficacy	4.75 (0.45)	4.63 (0.60)	4.63 (0.50)		
Beliefs about medicines					
Necessity	22.76 (2.52)	22.03 (3.03)	22.42 (2.32)	p = 0.008	p = 0.009
Concerns (medication)	10.47 (4.09)	11.08 (3.75)	11.21 (3.96)		
Illness perceptions					
Consequences	7.64 (2.56)	7.29 (2.59)	6.87 (2.65)	p = 0.016	
Timeline	8.01 (1.81)	8.21 (1.84)	7.80 (2.08)		
Personal control	7.64 (2.15)	7.81 (1.63)	7.94 (1.70)		
Treatment control	8.99 (1.13)	9.00 (1.09)	8.81 (1.41)		
Identity	2.69 (2.44)	2.93 (2.45)	3.17 (2.75)		
Concerns (rejection)	5.72 (2.86)	5.74 (3.10	5.32 (3.07)		
Coherence	7.39 (2.34)	7.61 (2.27)	7.17 (2.80)		
Emotional response	3.89 (3.04)	3.47 (2.85)	3.21 (2.81)	p = 0.033	

Prediction of Nonadherence

In step 1, the relationships between sociodemographic and medical characteristics were explored. These analyses showed that younger age (P = .03) and being in paid employment (trend, P = .06) were related to greater nonadherence. Pearson residuals were saved from this analysis and used as the dependent variable for the subsequent step (this procedure is equivalent to blocks in hierarchical regression). In step 2, controlling for age and employment, the psychological variables were entered. Nonsignificant ($p > .05$) variables were subsequently removed in a backward procedure. In the final parsimonious model, time, and the interaction between time and goal importance were significantly related to adherence categorization (see Table 3). There was no main effect of goal importance, however, as the interaction term is nested in this variable it was not removed from the model. To gain better understanding of this relationship, we divided goal importance according to the median split and plotted participants categorized as nonadherent per time point (Figure 1). The figure shows that participants who scored low on goal importance were more likely to become nonadherent over time.

Table 3. Multilevel logistical regression with IMNA as outcome

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	0.106	0.3256	-0.532	0.745	0.107	1	0.744
Time	0.616	0.1817	0.260	0.972	11.501	1	0.001
GI	-0.034	0.0703	-0.172	0.104	0.233	1	0.629
Time* GI	-0.127	0.0391	-0.204	-0.051	10.630	1	0.001

GI = Goal Importance

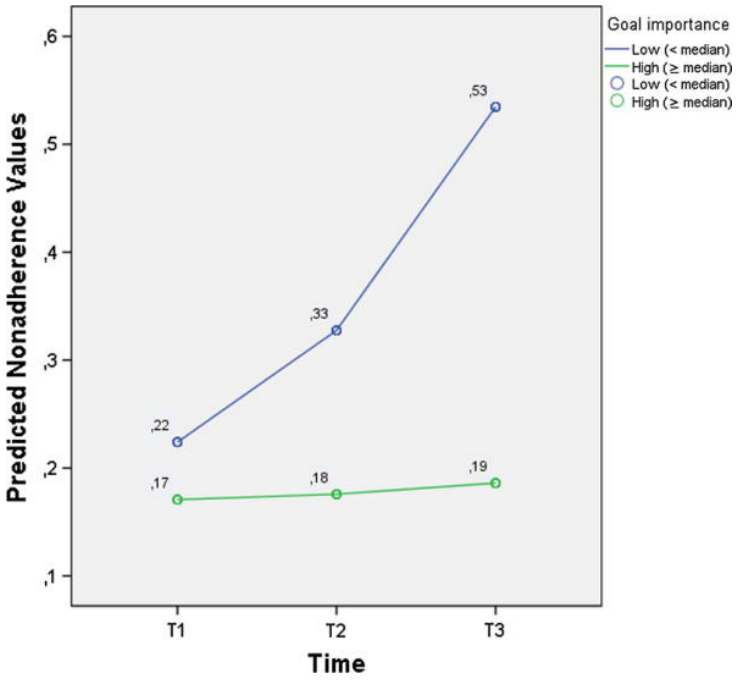


Figure 1. This figure demonstrates the predicted nonadherence values at each time point for participants who scored either high or low on goal importance.

Discussion

Illness and treatment perceptions in the first 18 months after kidney transplant can be described as functional. Adherence was seen as an important personal goal, well integrated with other goals (as indicated by low goal conflict), and self-efficacy to achieve the goal was high. Patients reported high-perceived necessity and had relatively few concerns about their immunosuppressive medication. Transplantation was reported to have a large impact

on patients' lives, however, this diminished over time. There was a good understanding of the transplant process, high personal and treatment control, low symptoms, and emotional response to the transplant. The latter further reduced over time. Concerns about rejection were fairly common; however, patients believed that the graft would last a relatively long time. This may reflect the large proportion of participants that received a living donor kidney (some preemptively), which in general has greater longevity than a deceased donor kidney.

These functional illness and treatment perceptions were inconsistent with the behavioral findings. Nonadherence was pervasive and increased significantly over time with almost one third of participants categorized as nonadherent at 18 months after transplantation. There appears therefore to be a discrepancy between the way in which patients perceive the transplantation and medication on the one hand and their medication taking behavior on the other. These findings support those of Lennerling and Forsberg(18) that there is no relationship between beliefs about immunosuppressive medication and adherence in kidney transplant recipients. We add that perceptions about the transplant, such as personal and treatment control over graft functioning were unrelated to adherence behavior. These findings highlight the disease and treatment specificity of perceptions.(30) A previous study that focused on promoting self-efficacy after kidney transplantation was ineffective in increasing adherence over and above the increases found in the control group.(31) Our findings may help explain this as self-efficacy was generally high and unrelated to nonadherence over time.

Of the psychological variables investigated, importance of adherence as a personal goal was related to adherence. Participants who scored low on goal importance were more likely to become nonadherent over time. Exploring patients' personal goals (such as work, relationships, and health) and the relative importance and integration of self-management goals could be one way of promoting adherence after transplantation. Few interventions have been effective in stimulating greater adherence in transplant patients.(32) Personal goal cognitions and self-regulatory skills may also be potential targets for adherence-enhancing interventions. Goal cognitions including perceived goal ownership, difficulty, support from the environment, and timeframe for achievement. Goal pursuit or self-regulatory skills include goal setting, planning, monitoring, revision, and emotion regulation.(33) There is a clear need for studies investigating the development and testing of adherence-promoting interventions after transplantation.

One of the strengths of this study is the prospective design, which allows consideration of how perceptions and behavior change over time. A number of limitations can also be highlighted. The patients captured in this study may not represent all patients due to exclusion, nonresponse, and attrition rates. Inclusion bias may have influenced our findings because 21% (44/212) of the potential participant pool did not satisfy the inclusion criteria.

Patients were required to speak sufficient Dutch to be included, and this was the largest group that was excluded. Further research is needed to explore predictors of nonadherence in these hard-to-reach groups, such as those who do not speak the dominant language, are illiterate, or have low health literacy. Thirty-three percent (55/168) declined to participate due to lack of interest or ill health; however, given the lack of difference in socio-demographic or medical characteristics between responders and nonresponders, we have no reason to believe this influenced the findings. A further 26% (29/113) of participants dropped out during the study, mainly for health reasons, which remains an issue when studying chronically ill patients. Regarding the method of assessing adherence, we focused on a self-report measure. Adherence is notoriously sensitive to method of measurement, and there is no gold standard.(21) In this study, we expected that self-reported adherence would have the largest relationship with illness and treatment perceptions, and this guided our choice to focus on self-report. Future studies could consider triangulation of findings from multiple, valid, and subjective and objective measures. Finally, we recognise that we focussed exclusively on patient-related factors.(34) In the future, a broader investigation into modifiable health system, social economic, condition, and therapy-related factors is likely to uncover other potential targets for promoting adherence after transplantation.

With regard to the clinical implications of our findings, clinicians are advised to take a holistic view to adherence support after kidney transplantation with attention for important personal goals and how medication taking fits into the patient's life. Clinical interactions and interventions often focus on the provision of medical information and education, which although important, is insufficient to bring about behavioral change.(32) Motivational interviewing is one potential tool that could be used to promote importance of adherence as a personal goal.(36,37) Exploring and helping maintain high motivation for medication adherence may help prevent deteriorating adherence over time. Given time restrictions of doctors and the psychosocial nature of this issue, it is likely that nurse practitioners could play an important role in offering this self-management support.(35) Finally, (barriers to) medication adherence should be something clinicians routinely explore not only immediately after transplantation but also longer after transplantation as our findings showing adherence is likely to deteriorate over time.

Acknowledgments

The authors would like to thank the individuals who participated in the study and the data managers who supported data collection.

References

1. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int 2001; 60(4):1565–1570.
2. Nevins TE, Thomas W. Quantitative patterns of azathioprine adherence after renal transplantation. Transplantation 2009;87(5):711–8.
3. Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. Transplantation 2014.
4. Butler JA, Peveler RC, Roderick P, Smith PWF, Horne R, Mason JC. Modifiable risk factors for non-adherence to immunosuppressants in renal transplant recipients: a cross-sectional study. Nephrol Dial Transplant 2004;19(12):3144–9.
5. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. Am J Transplant 2009;9(11):2597–606.
6. Dew MA, DiMartini AF, De Vito Dabbs A, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. Transplantation 2007;83(7):858–73.
7. Gaynor JJ, Ciancio G, Guerra G, et al. Graft failure due to noncompliance among 628 kidney transplant recipients with long-term follow-up: a single- center observational study. Transplantation 2014;97(9):925–33.
8. De Geest S, Denhaerynck K, Dobbels F. Clinical and economic consequences of non-adherence to immunosuppressive drugs. In: Grinyó J, ed. International Transplantation Updates Barcelona, Spain: Permanyer Publications; 2011.
9. Hagger MS, Orbell S. A meta-analytic review of the common-sense model of illness representations. Psychol Health 2003;18(2):141–84.
10. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self- regulation of health and illness. In: Cameron LD, Leventhal H, eds. The self-regulation of health and illness behaviour London: Routledge; 2003:42–65.
11. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 1999;47(6):555–67.
12. Broadbent E, Donkin L, Stroh JC. Illness and treatment perceptions are associated with adherence to medications, diet, and exercise in diabetic patients. Diabetes Care 2011;34(2):338–40.
13. Chilcot J, Wellsted D, Farrington K. Illness representations are associated with fluid nonadherence among hemodialysis patients. J Psychosom Res 2010;68(2):203–12.
14. O'Connor SM, Jardine AG, Millar K. The prediction of self-care behaviors in end-stage renal disease patients using Leventhal's Self-Regulatory Model. J Psychosom Res 2008;65(2):191–200.
15. Chisholm-Burns M, Pinsky B, Parker G, et al. Factors related to immunosuppressant medication adherence in renal transplant recipients. Clin Transplant 2012;26(5):706–13.
16. Kung M, Koschwanez HE, Painter L, Honeyman V, Broadbent E. Immunosuppressant nonadherence in heart, liver, and lung transplant patients: associations with medication beliefs and illness perceptions. Transplantation 2012;93(9):958–63.
17. Hugon A, Roustit M, Lehmann A, et al. Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. Transplantation 2014;27(2):222–8.
18. Lennerling A, Forsberg A. Self-reported non-adherence and beliefs about medication in a Swedish kidney transplant population. Open Nurs J 2012;6:41–6.
19. Massey EK, Tielen M, Laging M, et al. The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: a cohort study. J Psychosom Res 2013;75(3): 229–34.

20. Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients: an overview of instruments developed to date. Pharmacoeconomics 2007;25(4):269–86.
21. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999;21: 1074–90.
22. Glass TR, De Geest S, Weber R, et al. Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study. J Acquir Immune Defic Syndr 2006;41:385–92.
23. Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. AIDS 2002;16(2):269–77.
24. Pomaki G, Maes S, ter Doest L. Work conditions and employees' self-set goals: goal processes enhance prediction of psychological distress and well-being. Pers Soc Psychol Bull 2004;30(6):685–94.
25. Karoly P, Ruehlman LS. Goal cognition and its clinical implications: development and preliminary validation of four motivational assessment instruments. Assessment 1995;2(2):113–29.
26. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006;60(6):631–7.
27. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health 1999;14(1):1–24.
28. Little RJA, Rubin DB. Statistical analysis with missing data New York: John Wiley and Sons; 1987.
29. Tielen M, van Exel J, Laging M, et al. Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study. J Transplant 2014;2014:675301.
30. Heijmans M, de Ridder D. Assessing illness representations of chronic illness: explorations of their disease-specific nature. J Behav Med 1998; 21(5):485–503.
31. De Geest S, Schäfer-Keller P, Denhaerynck K, et al. Supporting medication adherence in renal transplantation (SMART): a pilot RCT to improve adherence to immunosuppressive regimens. Clin Transplant 2006; 20(3):359.
32. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. Transpl Int 2009;22(8):780–97.
33. Austin JT, Vancouver JB. Goal constructs in psychology: structure, process, and content. Psychol Bull 1996;120:338–75.
34. Sabate E. Adherence to long term therapies: evidence for action Geneva: World Health Organisation; 2003.
35. Peeters MJ, van Zuilen AD, van den Brand JAJG, et al. Nurse practitioner care improves renal outcome in patients with CKD. J Am Soc Nephrol 2014;25(2):390–8.
36. Garcia-Llana H, Remor E, del Peso G, Celadilla O, Selgas R. Motivational interviewing promotes adherence and improves wellbeing in pre-dialysis patients with advanced chronic kidney disease. J Clin Psychol Med Settings 2013;21(1):103–15.
37. Williams A, Manias E, Walker R, Gorelik A. A multifactorial intervention to improve blood pressure control in co-existing diabetes and kidney disease: a feasibility randomized controlled trial. J Adv Nurs 2012; 68(11):2515–25.

7

Attitudes to Medication after Kidney Transplantation and Their Association with Medication Adherence and Graft Survival: A 2-year Follow-Up Study

Mirjam Tielen[1], Job van Exel[2], Mirjam Laging[1], Denise K. Beck[1], Roshni Khemai[1], Teun van Gelder[1,3], Michiel G.H. Betjes[1], Willem Weimar[1], and Emma K. Massey[1].

[1] Department of Internal Medicine, Erasmus Medical Centre, P.O.Box 2040, 3000 CA Rotterdam, The Netherlands.

[2] Institue of Health Policy & Management (iBMG), Erasmus University Rotterdam, P.O.Box 1738, 3000 DR Rotterdam, the Netherlands.

[3] Department of Hospital Pharmacy, Erasmus Medical Centre, P.O.Box 2040, 3000 CA Rotterdam, The Netherlands.

Journal of Transplantation 2014: Article ID 675301

Abstract

Background: Nonadherence to medication is a common problem after kidney transplantation. The aim of this study was to explore attitudes towards medication, adherence and the relationship with clinical outcomes. Findings could inform development and tailoring of education and intervention programmes.

Method: Kidney recipients were invited to participate in a Q-methodological study 6 weeks after transplantation. As a measure of medication adherence, respondents completed the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS©-interview). Moreover, the intra-patient variability in the pharmacokinetics of tacrolimus was calculated, which measures stability of drug intake. Data on graft survival was retrieved from patient records up to 2 years after transplantation.

Results: 113 renal transplant recipients (19-75 years old) participated in the study. Results revealed three attitudes towards medication adherence: attitude 1; "Confident & Accurate", attitude 2; "Concerned & Vigilant", and attitude 3; "Appearance oriented & Assertive". We found association of attitudes with intra-patient variability in pharmacokinetics of tacrolimus, but not with self-reported nonadherence or graft survival. However, self-reported nonadherence immediately after transplantation was associated with lower two-year graft survival.

Conclusion: These preliminary findings suggest that nonadherence shortly after kidney transplantation may be a risk factor for lower graft survival in the years to follow. The attitudes to medication were not a risk factor.

Introduction

Kidney transplant patients are required to take lifelong immunosuppressive medication to prevent graft rejection. Nonadherence to immunosuppressive medication is a common issue and increases over time. Both dosage and timing of medication are crucial. Failure to take the medication as prescribed is a risk factor for (late) acute rejection, (late) graft failure/loss, and patient mortality (1-4).

Among renal transplant patients, on average 36% of patients per year are reported to be nonadherent to immunosuppressive medication with estimates ranging from 2 to 67% (2, 5-7). A number of patient, practitioner and regime related factors have been shown to be related to adherence after renal transplantation. The number and frequency of medication, as well as the relationship, communication and trust between the patient and health care provider are likely to influence adherence (3). Nonadherence is particularly a problem among adolescent transplant recipients. Rates of nonadherence have also found to be related to factors such as level of social support, education and socioeconomic status (3, 8). There is also evidence that nonadherence prior to transplantation is an independent predictor of nonadherence after transplantation (5, 9).

As nonadherence is a behavioral rather than a medical issue, many studies have focused on exploring possible psychological and other modifiable predictors (2, 3, 10). Psychological well-being, such as depression, can affect the extent to which an individual is adherent to the medication regime (11). In a previous study we reported clusters of attitudes which may indicate risk of poorer adherence to medication among young adult renal transplant patients (12). This was a population of young adults who had varying time since transplantation. Evidence suggests that adherence immediately after transplantation is often high but gradually declines over time (2), although some authors suggest nonadherence might be 'early and pervasive' among renal transplant patients (4). Schmid-Mohler et al. (10) used the integrative model of behavioral prediction and found that forgetfulness/interruption of daily routine was the only significant predictor for non-adherence. In their later work (13) they found that nonadherence was significantly associated with patients beliefs about their immunosuppressive medicines. The aim of this study was to gain greater insight into attitudes towards the immunosuppressive medication regime shortly after kidney transplantation. And what is the relationship with adherence to medication and clinical outcomes in the years subsequent to transplantation.

Methods

Participants

All consecutive patients who received either a living or deceased donor kidney transplant in the Erasmus Medical Centre, Rotterdam, between August 2010 and October 2011 were invited to participate in the study. The inclusion criteria required that kidney transplant patients were older than 18 years, had a functioning graft six weeks post-transplant and had a sufficient level of understanding and speaking of the Dutch language. For clinical endpoints we had a follow-up time of at least two years after transplantation (until 31th of Oct 2013).

All participants provided written consent for participation and the study was approved by the Medical Ethics Committee of the Erasmus Medical Centre.

Measures and procedure

To explore attitudes towards medication after kidney transplantation we used Q-methodology. This is a method that combines aspects of qualitative and quantitative methods and provides a foundation for the systematic study of subjectivity (e.g., peoples' viewpoints or beliefs, in this case attitudes to the immunosuppressive medication regime after kidney transplantation) (14, 15). The results of a Q-methodological study can be used to describe a population of viewpoints, not a population of people (16, 17). In previous studies we generated statements for young adults and elderly using the WHO dimensions of adherence (8, 18): socioeconomic-related factors, health care team or health system-related factors, condition-related factors, treatment-related factors and patient-related factors. This was done based on an iterative procedure and consensus (12). For the current study the statements were tailored for more general use with patients of all ages. The final Q-set consisted of 37 statements (Table 1), which were randomly numbered and printed on cards.

Respondents were invited to participate in face-to-face interviews. Patients were interviewed at 6 weeks after transplantation during which they were asked to rank-order the 37 statements, using a quasi-normal grid ranging from -3 to +3 (Figure, see page 21) (12). In addition, participants were asked to explain the ranking of the 2 statements that they agreed with (+3) and disagreed (-3) the most. The individual rankings of statements were analysed using by-person factor analysis so as to reveal a limited number of corresponding patterns in the way the statements were sorted by respondents. Correlation between individual rankings of statements is viewed as an indication of similarity in attitude.

Table 1. Statements and factor scores

Statements	Post transplant attitudes		
	Factor 1	Factor 2	Factor 3
1. I would rather not tell others that I have a transplant	-2	-2	-3
2. If you forget your medication now and then, it's not a problem	-1	-3**	-1
3. It is more important to enjoy life than to be compliant	0**	-2*	-1*
4. If I do something that is not so healthy I tend to feel guilty	-1**	0	0
5. I don't want my life to revolve around my disease	+1*	+2*	+3**
6. I don't like to take medication when others are around	-1**	-2**	0**
7. I have a healthy lifestyle	0	0	0
8. I am worried that my kidney will be rejected	0*	+3**	0*
9. I am concerned about my future	-3**	0**	-1**
10. I'm scared I will have to go on dialysis (again)	-1**	+2**	-3**
11. My appearance is not very important to me	0**	-1**	-2**
12. I struggle with the fact that my medication makes me fatter	-1**	0**	+1**
13. I often feel gloomy and depressed	-3**	-1**	-1**
14. I have side-effects from my medication	-1**	0**	+2**
15. I can manage my own medication and appointments	+1**	+1**	+3**
16. My loved ones interfere too much with my health	-1	-1	-1*
17. I receive enough support from friends and/or family	+2	+1**	+2
18. I would like to meet other kidney transplant patients	0	-1	0**
19. I appreciate it when others remind me to take my medication	0	0**	0
20. I am extra careful with this kidney because it's from a loved one	+2**	+2**	-1**
21. I don't mind taking multiple medications a day	+1**	0	0
22. When I sleep in, I just take my medication later	0**	-1**	-2**
23. I have problems swallowing larger pills	-2	-1	-1
24. I sometimes forget my medication	-2	-3*	-2
25. I know what my medications do	+1	0	+1
26. I have a regular daily routine	0	0	0*
27. A pillbox is a handy aid	+2	0**	+1
28. I want the medication to stay the same if I feel good	0	-1**	0
29. I take my immunosuppressive drugs exactly every twelve hours	+3**	+1	+1
30. I find it reassuring to have my medication with me when I am away from home	0	+1	+1
31. If I'm not sure whether I have already taken my pills, I just take it again	-2	-2	-2
32. The doctors know what is best for me	+1**	+1	0
33. If I don't comply with the regime, it's ok for healthcare professionals to confront me with the consequences	+2	+2	+1*
34. I find it reassuring that they check my kidney functioning regularly at the outpatient clinic	+3*	+3	+2
35.I like it when the doctor gives me a say in the treatment	+1*	+1*	+2*
36. I am honest with the doctor about my medication intake	+1	+1**	+1
37. If I take a wrong dose of medication I let my doctor know	0	0	0

Note: * p<.05; ** p<.01. A '-3' score indicates that a typical kidney transplant patient with that post-transplant attitude would disagree most with that statement, a '+3' score that (s)he would agree most.

The outcome variable was nonadherence. To study nonadherence effectively we used a combination of measurement methods, as proposed by Farmer (19). Firstly, we used the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS©-interview) (20, 21). This scale is a self-report instrument that consists of 4 questions on the taking and timing of medication, drug holidays, reduction of the dose and persistence over the past month (Table 2). An affirmative answer to any of the first 4 questions results in assignment to the nonadherent group. This scoring is intentionally strict due to an assumption of under-reporting of nonadherence. Patients also rated their own adherence using a Visual Analogue scale from 0% (medication never taken as prescribed) to 100% (medication always taken as prescribed). The BAASIS measure was selected as it is short, reliable, valid and sensitive to both timing and taking which is of particular importance for the immunosuppressive regime after kidney transplantation (20). A number of studies have demonstrated support for the validity of both parts of the instrument (22, 23). Specificity and sensitivity of the visual analogue scale have been shown to be high (22).

Table 2: Adherence 6 weeks after transplantation as measured with the BAASIS© interview[a] (n=113).

Part 1[b]		Response n (%)	Categorized as nonadherent n (%)
1a	Taking dimension: Do you remember missing a dose of your immunosuppressive medication (IM) in the past 4 weeks?		9 (8.0)
	▪ Once	8 (7.1)	
	▪ 2-3 times	1 (0.9)	
1b	Drug holidays: Do you remember having skipped two or more doses of your IM in a row in the past 4 weeks?	0	
2	Timing dimension: Do you remember having taken your IM more than 2 h before or after the prescribed dosing time in the past 4 weeks?		12 (10.6)
	▪ Once	10 (8.8)	
	▪ 2-3 times	1 (0.9)	
	▪ 4-5 times	1 (0.9)	
3	Reduction of dose: Have you altered the prescribed amount of your IM during the past 4 weeks without your doctor telling you to do so?	0	
4	Persistence: Have you stopped taking your IM completely in the past 4 weeks without your doctor telling you to do so?	0	
Total			19 (16.8)
Part 2[c]		median (range)	
5	Overall adherence rating	100 (77-100)	

Note: [a] © University of Basel, Leuven-Basel Adherence Research Group, Institute of Nursing Science, University of Basel, Belgium, 2005. Permission & conditions to use the BAASIS® can be obtained from sabina.degeest@unibas.ch. [b] Response categories for questions 1 to 4 are given on a 6-point scale: (0) no; (1) once; (2) 2-3 times; (3) 4-5 times; (4) every 2-3 days; (5) almost daily. [c] Visual Analogue scale ranging from 0% (medication never taken as prescribed) to 100% (medication always taken as prescribed).

Secondly, we calculated patient intra-individual variability in the pharmacokinetics of immunosuppressive medication, in this case tacrolimus (Prograft®) (24). Whole blood tacrolimus concentrations in different measurements over time within patients were used to calculate intra-individual variability. Patients with a high intra-patient variability have tacrolimus concentrations that are often outside the therapeutic window. Under-exposure may lead to immune activation, and over-exposure can result in CNI-induced nephrotoxicity. Both could affect long-term outcome. Borra et al.(24) showed that high intra-individual variability in the pharmacokinetics of tacrolimus leads to reduced graft survival. One of the most likely causes for intra-patient variability is medication nonadherence. To calculate the intra-patient variability in tacrolimus concentrations we used the method previously described by Borra et al (24).

For the clinical endpoints, we collected information about rejection (yes/no) and graft failure (yes/no) two years after transplantation.

Statistical analysis

Independent t-tests and chi-squared analyses were conducted to test differences between responders and non-responders. As the BAASIS overall rating scale was negatively skewed, a Mann-Whitney test was used to test the difference on this scale between adherent and nonadherent patients. One-way ANOVA and chi-squared tests were used to test the association between attitudes and adherence. When cell values were small, fisher's exact tests were used to test 2x2 associations. Survival analyses were calculated with Kaplan-Meier and lifetable. Analyses were carried out using the Statistical Package for Social Sciences, version 20.0. Q-methodological data were analysed using PQMethod 2.11 (Schmolck & Atkinson, 2002).

Results

Demographic characteristics

Between August 2010 and October 2011, 212 kidney transplantations were carried out in our centre. Of these 212 patients 44 were excluded for the following reasons: not able to speak the Dutch language sufficiently (n=23), a mental or physical disability (n=9); death prior to inclusion (n=4); graft loss (n=4), primary non-function (n=3) and follow-up at another centre (n=1). Of the 168 kidney patients who were eligible to participate, 113 patients were included (67.3%). Fifty-five kidney transplant patients (32.7%) did not want to participate because they were not interested (n=20) or did not want to stay longer at the outpatient clinic for the study (n=26). Seven did not want to participate for logistical reasons and 2 were

discontent with their treatment and decided not to participate. Demographic characteristics of respondents and non-respondents are shown in Table 3. Of the 113 participants we had a minimum follow-up of two-years; 35 experienced graft rejection and 5 graft failures (1 unknown, 4 due to rejection) and 6 patients died with a functioning graft.

Table 3: Patient characteristics of respondents and non-respondents

	Respondents (n=113)	**Non-respondents (n=55)**	
Demographics	**n (%)**	**n (%)**	**p-value**
Age (years)			
18-29	9 (8%)	5 (9.1%)	0.804
30-45	27 (23.9%)	8 (14.5%)	0.161
46-64	59 (52.2%)	34 (61.8%)	0.240
65+	18 (15.9%)	8 (14.5%)	0.816
Gender			
Male	73 (64.6%)	37 (67.3%)	0.733
Female	40 (35.4%)	18 (32.7%)	
Education level			
High	22 (19.5%)	5 (9.1%)	0.134
Middle	64 (56.6%)	28 (50.9%)	0.940
Low	27 (23.9%)	17 (30.9%)	0.180
Unknown		5	
Ethnicity			
Caucasian	86 (76.1%)	40 (72.7%)	0.489
Asian	9 (8%)	4 (7.3%)	0.851
African	10 (8.8%)	4 (7.3%)	0.705
Turkish	2 (1.8%)	3 (5.4%)	0.195
Other	2 (1.8%)	3 (5.4%)	0.195
Unknown	4	1	
Kidney transplant			
Living donor	89 (78.8%)	42 (76.4%)	0.725
Deceased donor	24 (21.2%)	13 (23.6%)	0.690
Number of transplants (median, range)	1 (1-5)	1 (1-3)	
Marital status			
Married	69 (61%)	28 (50.9%)	0.161
Living together	14 (12.3%)	5 (9.1%)	0.502
Single	16 (14.2%)	19 (34.5%)	**0.003**
Divorced	8 (7.1%)	1 (1.8%)	0.149
Widow/widower	2 (1.8%)	1 (1.8%)	0.994
Other	4	1	

Attitudes

The analysis of the Q-methodological study revealed three distinct attitudes towards medication adherence (Table 1). Of the 113 participants 23 did not load significantly on any of these attitudes, or on more than one. Of the remaining 90 participants 40 patients defined factor 1, 38 factor 2 and 12 factor 3.

Patients defining the first factor find it important to take their medication exactly every twelve hours (statement 29). They take good care of their kidney (statement 20) and have no worries about the future (statement 9) and are not afraid they have to go on dialysis again (statement 10). They find it reassuring their kidney function is checked regularly (statement 34); these patients feel the least gloomy or depressed (statement 13). They do not mind taking multiple medicines every day (statement 21) but also indicate not to experience many side-effects (statement 14). This factor was labeled "Confident & Accurate". These quotes from participants defining this factor illustrate this attitude profile: *"this kidney was given to me by my wife, I have an obligation to take good care of this kidney"*; "*You don't have any influence on things going wrong; I will do the best I can".*

Patients defining the second factor also found it reassuring that their kidney function is checked regularly (statement 34), but this is more out of fear of graft loss. They are concerned that their kidney will be rejected (statement 8) and are afraid to go (back) on dialysis (statement 10). Therefore they are careful and they do not think it is wise to forget medication, even if it is only now and then (statement 2). They would rather be adherent than to enjoy their life to the fullest (statement 3). This factor was labeled 'Concerned & Vigilant'. These quotes illustrate this attitude: *"I'm always so worried, after my check-up I always call my doctor for the test results"; "Rejection is always on my mind, this has an impact on my life"; "It is so important to stay focused on the regime, I don't want to blame myself for ruining this kidney, you have to follow the rules"*.

Patients defining the third factor find their appearance important (statement 11) and are afraid that the medication will influence their appearance negatively (statement 12). They do not want their lives to revolve around their disease (statement 5), although they indicate experiencing side effects (statement 14). Nevertheless they do not feel the need to be extra careful with their kidney from a loved one (statement 20), and they are not really concerned they will have to go (back) on dialysis (statement 10). They want their own say in their treatment (statement 35) and feel they are able to manage their medication and appointments themselves (statement 15). Therefore this factor was labeled 'Appearance oriented & Assertive'. These quotes illustrate this attitude: *"I don't feel sick, not everybody knows I have a kidney transplant"; "I have been a kidney patient for 40 years now, and I want to be involved"; "In the future I want to do things without thinking about my disease"; "This kidney is from my mum and that is special to me, but I am not extra careful with my kidney because it is from my mum".*

There was general consensus between participants regarding a number of statements. In none of the attitudes patients were ashamed of their transplantation, minded others knowing about their kidney transplant (statement 1), or experienced problems with

swallowing larger pills (statement 23). All attitudes were neutral about having a healthy lifestyle (statement 7), taking their medication with them when they go out of the house (statement 30) and letting the doctor know if they took a wrong dose of the medication (statement 37).

Adherence

The BAASIS-interview revealed that six weeks after transplantation, 17% (n=19) were classified as nonadherent (missed a dose or >2 hours earlier or later than prescribed in the past 4 weeks). Nine patients (8%) had missed a dose in the past month. Twelve patients (11%) had taken their dose 2 hours before or after the prescribed time; and two patients had either missed a dose or taken their dose 2 hours before or after the prescribed time. None of the patients had altered their dose or completely stopped taking their medication in the past four weeks (Table 2). Demographic characteristics of the self-reported nonadherent patients versus the self-reported adherent patients are shown in Table 4. There were no significant differences in age, gender, education level, donor kidney, ethnicity or social status between these groups.

Patients also rated their own overall adherence from 0 to 100%. A Mann-Whitney test revealed a significant difference between groups: the adherent group had a median of 100% and the nonadherent group had a significantly lower median of 95% ($p < .01$).

Of the 19 patients who were classified as nonadherent, 8 patients loaded on attitude 1, 4 patients on attitude 2, 2 patients on attitude 3 and 5 patients did not load on any specific attitude. There was no significant association between attitudes and self-reported nonadherence classification ($X^2(2)= 1.344$ $p=.476$).

In order to calculate the intra-patient variability in tacrolimus we used a minimum of 3 tacrolimus measurements per patient (n=4) and a maximum of 5 measurements per patient (n=87). For 7 patients we were not able to calculate the intra-patient variability because of missing data. The median intra-patient variability was 14.5% (range 1.12-86.3%). As a cut-off we divided the group in tertiles and split the patients into a group with low intra-patient variability (the patients in the lowest tertile 0-11.7%) and a group with high variability (the patients in the highest tertile, 18.02-100%). This resulted in 34 patients in the low-variability group, with a mean variability of 8.9%, and 35 patients with high-variability, with a mean variability of 27.0%. The intra-patient variability was significantly correlated with attitude profile ($X^2(2)= 6.799$ $p=.036$). Patients with a high variability loaded more often on the attitude “Concerned & Vigilant”, while those with a low variability loaded more often on the attitude “Confident & Accurate”. Intra-patient variability was not correlated with the BAASIS classification of adherent versus nonadherent patients ($X^2(1)= 2.88$ $p=.110$).

Table 4: Demographics self-reported nonadherent versus adherent patients

	Nonadherent (n=19)	Adherent (n=94)	
Demographics	**n (%)**	**n (%)**	**p-value**
Age (years)			
18-29	2 (10.5%)	7 (7.4%)	0.651
30-45	3 (15.8%)	24 (25.5%)	0.364
46-64	11 (57.9%)	48 (51.1%)	0.587
65+	3 (15.8%)	15 (16%)	0.985
Gender			
Male	11(57.9%)	62 (66%)	0.503
Female	8 (42.1%)	32 (34%)	
Education level			
High	2 (10.5%)	20 (21.3%)	0.280
Middle	12 (63.2%)	52 (55.3%)	0.529
Low	5 (26.3%)	22 (23.4%)	0.786
Ethnicity			
Caucasian	15 (78.9%)	71 (75.5%)	0.995
Asian	0 (0%)	9 (9.6%)	0.150
African	3 (15.8%)	7 (7.4%)	0.272
Turkish	0 (0%)	2 (2.1%)	0.512
Other	1 (5.3%)	1 (1.1%)	0.220
Unknown	0	4	
Kidney transplant			
Living donor	16 (84.2%)	73 (77.7%)	0.524
Deceased donor	3 (15.8%)	21 (22.3%)	
Number of transplant (median, range)	1 (1-2)	1 (1-5)	1.000
Marital status			
Married	12 (63.2%)	57 (60.6%)	0.837
Living together	0 (0%)	14 (14.9%)	0.072
Single	4 (21.1%)	12 (12.8%)	0.345
Divorced	1 (5.3%)	7 (7.4%)	0.735
Widow/widower	1 (5.3%)	1 (1.1%)	0.205
Other	1 (5.3%)	3 (3.2%)	0.656

Clinical endpoints

Patients that reported nonadherence in the BAASIS©-interview (n=19) had a lower two-year graft survival (failure n=3) compared to the adherent group (failure n=2) (84% versus 98% respectively ($X^2(1)=6.409$ p=0.038). See Figure 2. Graft failure was not related to attitudes (p=0.532) or intra-patient variability (p=0.159). Patients with rejection (n=35) had no significantly lower graft survival (p=.167), graft rejection was not correlated with self-reported adherence ($X^2(1)=.004$ p=.574), the three attitudes ($X^2(2)=2.391$ p=.347) or intra-patient variability ($X^2(1)=2.947$ p=.074).

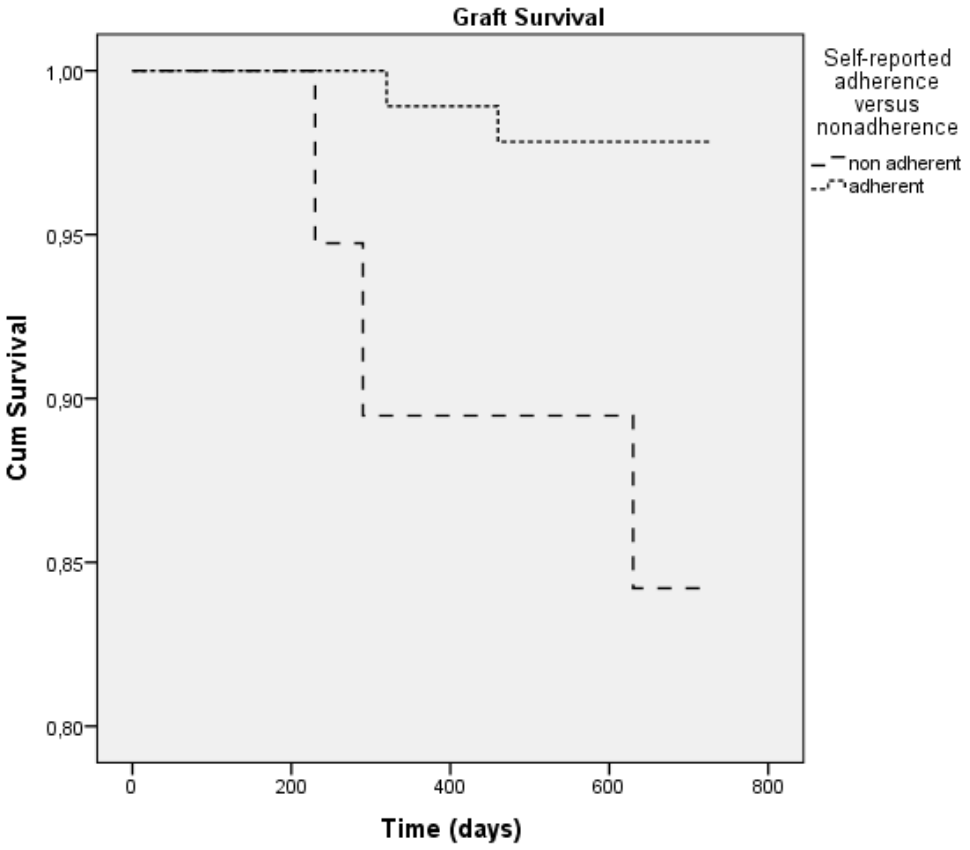


Figure 2: Kaplan Meier Graft survival. The nonadherent group consisted of 19 patients (3 graft failures) and the adherent group consisted of 94 patients (2 graft failures).

Discussion

This Q-methodological study revealed three distinct attitudes toward medication nonadherence as early as six weeks after transplantation: (1) Confident & Accurate, (2) Concerned & Vigilant, and (3) Appearance oriented & Assertive. We observed association between these attitudes, but not with self-reported adherence and clinical outcomes 2 years after transplantation. Patients with the attitude 'Confident & Accurate' appeared not to have any problems with medication adherence. They were confident about managing their medication regime 6 weeks after transplantation and these patients had significantly lower variability of tacrolimus in their blood. Earlier research has suggested that lower variability indicates greater adherence (24). In the attitude 'Concerned & Vigilant' we found evidence for a relationship between anxiety about the medication regime and nonadherence, as

indicated by the significantly higher variability of tacrolimus in the blood of these patients. DiMateo et al. (25) also found a difference in risk of nonadherence between anxious and non-anxious patients. They argued that patients were worried about their future and that this translated into frequent monitoring, fear of forgetting and non-compliance. In our study, significantly more patients with a high-intra patient variability loaded on this 'Concerned and Vigilant' attitude. These findings suggest that individuals characterised by anxiety about their medication regime may be less adherent or, alternatively, that patients who have more problems with their medication are more worried. This association between attitude and adherence was, however, only found when adherence was measured using levels of medication found in the blood, not when using self-report. Although the patients defining attitude 2 seem to indicate they are reliable in their medication taking, their intra-patient variability suggests differently. This discrepancy suggests potential under-reporting of nonadherence in this group on the self-report measure. Several studies before have found differences between self-reported nonadherence, which is simpler to measure but more susceptible to error, and direct measures for defining nonadherence such as drug levels or a clinical indicator, which are more objective and accurate but expensive (19, 26, 27). Patients with the attitude 'Appearance oriented & Assertive' want to live a normal life, be in control and think they are capable of taking care of their kidney, but are also the patients that indicate to experience side effects. Although their intra-patient variability of tacrolimus was not elevated, we speculate that these patients may have a higher risk of nonadherence in the future because they are concerned about (cosmetic) side effects of their medication regimen.

The Q-methodology study thus uncovered different attitudes towards medication adherence, which were associated with intra-patient variability of tacrolimus but not with self-reported nonadherence and with clinical endpoints such as graft rejection or graft survival. In contrast, self-reported nonadherence 6 weeks after transplantation was associated with graft failure in the subsequent 2-year period, but variability of tacrolimus was not.

The findings reported should be interpreted in the light of a number of limitations. Firstly, as discussed, there is a possibility of under-reporting of nonadherence given the clinical setting of the study and the possibility of socially desirable answers. The BAASIS scale was developed with this phenomenon in mind and is therefore intentionally strict in its scoring mechanism: even a small deviation in the regime leads to a classification as nonadherent (20). However, these scores were not associated with intra-patient variability of tacrolimus, a direct and potentially more objective measure for adherence, so that under-reporting cannot be dismissed. Secondly, patients who did not have sufficient mastery of the Dutch language were excluded and an other group of patients declined to participate. It is possible that these harder-to-reach patients demonstrate yet another attitude, not identified here.

Findings therefore cannot be generalised to these patients. Finally, this study was conducted among a limited number of patients in a single centre. Replication of this study in different centres, with particular attention to inclusion of the harder-to-reach patients as well, is therefore advised.

There are a few clinical implications of these findings. We found that Q-methodology was a useful tool for nurses in their interactions with patients, as it helped patients to talk freely about a difficult clinical topic. This approach offered patients the opportunity to (visually) structure their thoughts and nurse researchers the opportunity to investigate such pertinent issues in greater depth and to develop and tailor education programmes for this patient population. In any case, the finding that self-reported nonadherence was related to likelihood of graft failure suggests that a dialog between nurse and patient on medication adherence early in the transplant recovery period could be a useful tool to flag up individuals at risk of graft failure. Future research is also needed to further explore the (reciprocal) relationship between worry/anxiety and nonadherence and its clinical consequences.

Acknowledgments

This study was funded from an internal grant “Evidence Based Care Nurses” by the Erasmus University Medical Centre Rotterdam, The Netherlands.

References

1 H. Vlaminck, B. Maes, G. Evers et al., "Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients," *American Journal of Transplantation*, vol. 4, no. 9, pp. 1509–1513, 2004.

2 K. Denhaerynck, F. Dobbels, I. Cleemput et al., "Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review," *Transplant International*, vol. 18, no. 10, pp. 1121–1133, 2005.

3 M. Loghman-Adham, "Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation," *American Journal of Managed Care*, vol. 9, no. 2, pp. 155–171, 2003.

4 T. E. Nevins and A. J. Matas, "Medication noncompliance: another iceberg's tip," *Transplantation*, vol. 77, no. 5, pp. 776–778, 2004.

5 F. Dobbels, J. Vanhaecke, L. Dupont et al., "Pretransplant predictors of posttransplant adherence and clinical outcome: an evidence base for pretransplant psychosocial screening," *Transplantation*, vol. 87, no. 10, pp. 1497–1504, 2009.

6 M. A. Dew, A. F. DiMartini, A. De Vito Dabbs et al., "Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation," *Transplantation*, vol. 83, no. 7, pp. 858–873, 2007.

7 K. Laederach-Hofmann and B. Bunzel, "Noncompliance in organ transplant recipients: a literature review," *General Hospital Psychiatry*, vol. 22, no. 6, pp. 412–424, 2000.

8 WHO, *Adherence to Long-Term Therapies: Evidence for Action*, World Health Organization, Geneva, Switzerland, 2003.

9 M. A. Chisholm, G. M. Williamson, C. E. Lance, and L. L. Mulloy, "Predicting adherence to immunosuppressant therapy: a prospective analysis of the theory of planned behaviour," *Nephrology Dialysis Transplantation*, vol. 22, no. 8, pp. 2339–2348, 2007.

10 G. Schmid-Mohler, M. P. Thut, R. P. Wüthrich, K. Denhaerynck, and S. De Geest, "Non-adherence to immunosuppressive medication in renal transplant recipients within the scope of the integrative model of behavioral prediction: a cross-sectional study," *Clinical Transplantation*, vol. 24, no. 2, pp. 213–222, 2010.

11 D. Cukor, H. Newville, and R. Jindal, "Depression and immunosuppressive medication adherence in kidney transplant patients," *General Hospital Psychiatry*, vol. 30, no. 4, pp. 386–387, 2008.

12 M. Tielen, A. L. Van Staa, S. Jedeloo, N. J. A. Van Exel, and W. Weimar, "Q-methodology to identify young adult renal transplant recipients at risk for nonadherence," *Transplantation*, vol. 85, no. 5, pp. 700–706, 2008.

13 M. Chisholm-Burns, B. Pinsky, G. Parker et al., "Factors related to immunosuppressant medication adherence in renal transplant recipients," *Clinical Transplantation*, 2012.

14 R. M. Cross, "Exploring attitudes: the case for Q methodology," *Health Education Research*, vol. 20, no. 2, pp. 206–213, 2005.

15 S. Watts, P. Stenner, and Q. Ding, *Methodological Research*, Sage, London, UK, 2012.

16 A. Risdon, C. Eccleston, G. Crombez, and L. McCracken, "How can we learn to live with pain? A Q-methodological analysis of the diverse understandings of acceptance of chronic pain," *Social Science and Medicine*, vol. 56, no. 2, pp. 375–386, 2003.

17 N. W. Smith, *Current Systems in Psychology: History, Theory, Research, and Applications*, Operant Subjectivity, 2001.

18 M. Tielen, N. J. A. Van Exel, M. C. Van Buren, L. Maasdam, and W. Weimar, "Attitudes towards medication non-adherence in elderly kidney transplant patients: a Q methodology study," *Nephrology Dialysis Transplantation*, vol. 26, no. 5, pp. 1723–1728, 2011.

19 K. C. Farmer, "Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice," *Clinical Therapeutics*, vol. 21, no. 6, pp. 1074–1090, 1999.

20 F. Dobbels, L. Berben, S. De Geest et al., "The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review," *Transplantation*, vol. 90, no. 2, pp. 205–219, 2010.

21 I. Cleemput and F. Dobbels, "Measuring patient-reported outcomes in solid organ transplant recipients: an overview of instruments developed to date," *PharmacoEconomics*, vol. 25, no. 4, pp. 269–286, 2007.

22 J. C. Walsh, S. Mandalia, and B. G. Gazzard, "Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome," *AIDS*, vol. 16, no. 2, pp. 269–277, 2002.

23 T. R. Glass, S. De Geest, R. Weber et al., "Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study," *Journal of Acquired Immune Deficiency Syndromes*, vol. 41, no. 3, pp. 385–392, 2006.

24 L. C. P. Borra, J. I. Roodnat, J. A. Kal, R. A. A. Mathot, W. Weimar, and T. Van Gelder, "High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation," *Nephrology Dialysis Transplantation*, vol. 25, no. 8, pp. 2757–2763, 2010.

25 M. R. DiMatteo, H. S. Lepper, and T. W. Croghan, "Depression is a risk factor for noncompliance with medical treatment meta-analysis of the effects of anxiety and depression on patient adherence," *Archives of Internal Medicine*, vol. 160, no. 14, pp. 2101–2107, 2000.

26 L. De Bleser, F. Dobbels, L. Berben et al., "The spectrum of nonadherence with medication in heart, liver, and lung tranplant patients assessed in various ways," *Transplant International*, vol. 24, no. 9, pp. 882–891, 2011.

27 L. Osterberg and T. Blaschke, "Adherence to medication," *The New England Journal of Medicine*, vol. 353, no. 5, pp. 487–497, 2005.

8

Discussion

This thesis investigated immunosuppressive medication nonadherence after kidney transplantation; in particular the psychosocial aspects of nonadherent behavior. The goal was to gain knowledge that would help nurse practitioners in their daily practice. We gained greater insight into patients' medication taking behavior, the way patients perceive their illness and medication and how this medication regime fits into their daily lives.

The main research questions were:
(1) What is the rate of nonadherence among our population of kidney transplant recipients and does this change over time?
(2) What are the attitudes, beliefs and goals of kidney transplant recipients towards the medication regime?
(3) To what extent are these attitudes, beliefs and goals related to nonadherence?
(4) To what extent is nonadherence related to graft survival?
In the general discussion these questions will be addressed.

Nonadherence and clinical outcomes

The rate of nonadherence was consistent over the studies in this thesis. We found a nonadherence rate of 31% in our cross-sectional study with elderly where the median time after transplantation was 5 years, this is consistent with our findings in our later prospective studies in which we found a nonadherence rate of 31% after 18 months. Our findings are comparable to other studies among kidney transplant patients, describing nonadherence in approximately one third of the patients (1-3).

Nonadherence was found early after kidney transplantation. Our hypothesis was that patients who are recently transplanted are well informed and motivated to take their medication, but there was already a 17% nonadherence rate 6 weeks after transplantation. This is in line with other authors that suggest that nonadherence is 'early and pervasive' among kidney transplant patients (4). Moreover, the rate of nonadherence increased further over time. The perception of the necessity of medication decreases as time since transplantation goes by, as reported in chapter 6 (1, 5, 6). In our prospective studies we found that timing issues, as opposed to taking issues, were the most commonly reported form of nonadherence. Kidney transplant patients are required to take their immunosuppressive medication on time every 12 or 24 hours. Barriers to taking medication can include the complexity of the regime. The higher the number of pills or the more taking moments during the day, the more difficult it will be to be adherent (7, 8). Side effects can play a role in nonadherence but also, depression, younger age, health literacy, lack of understanding, patient beliefs, or having a living donor kidney (2, 9-12). Anxiety symptoms often co-occur with depressive symptoms (13). While depression is indicated as a risk factor for nonadherence (14-17), we found the opposite that the gloominess about future prospects

translated in a high need of control and adherence in young adult recipients (chapter 2). This is comparable to another study that found nonadherent young adult recipients had fewer symptoms of depression than adherent recipients (18). In one study they found intentional non-adherence that was related to depression (19). Most studies focus on unintentional nonadherence; e.g. practical barriers to adherence, forgetfulness and missing medication when one's routine is different (19-21). It is likely that patients forget medication to which they attach lower priority or importance to adherence.

In this thesis it is clear that nonadherence occurs amongst all groups of kidney transplant patients. Many studies have associated nonadherence with lower age and adolescence (12). This thesis showed that there is a significant difference in graft survival in young adults compared to older adults (chapter 2), nonadherence is likely to play a role in this although other factors may also contribute. We were able to categorize young adults that were suggested to be at risk of being nonadherent according to their attitude profile. Moreover each specific subgroup of young adults demands a specific tailored approach from a health care professional. Because this particular study was cross-sectional it had its limitations and we also did not measure adherence behavior. In addition to the findings on young adults (chapter 2), our studies also showed that in elderly patients (chapter 4) and in a cohort study of kidney transplant patients of all ages (chapters 5,6,7) nonadherence is present. Age alone is therefore not an accurate indicator of (non)adherence. We also found some young adults that were very adherent.

We demonstrated in chapter 7 that nonadherent patients according to the BAASIS scale also scored themselves lower on the overall adherence rating scale. Another study found the opposite between self-reported nonadherence according to the BAASIS (high) and the self-rating overall adherence (high) in young adults (18). This could be typical for young adults, we detected in interviews with young adults that they feel invulnerable to the effects of discontinuing immunosuppressive drugs and find it quite normal to take immunosuppressive drugs late and do not perceive any problem in doing so (chapter 3). Advantages of the BAASIS-interview or questionnaire are that it is a quick tool to asses self-reported non-adherence and it measures both taking and timing issues.

There is no gold standard for measuring nonadherence; we used self-report adherence scales (chapters 4 and 5,6,7) and intra-patient variability (chapter 7). The limitation of self-reported adherence is that patients could give socially desirable answers. In elderly patients (>65 years) we used the Siegal scale for self-reported non-adherence, this scale is limited to issues of taking medication but does not measure issues of the timing of medication. In contrast, the BAASIS is a validated scale and measures the taking, timing and dosing of the medication. It is therefore possible that we did not capture timing issues in elderly patients due to the Siegal scale as opposed to the BAASIS.

Better medication adherence improves health outcomes and results in lower healthcare costs (22, 23). Our findings suggest that nonadherence shortly after kidney transplantation may be a risk factor for lower graft survival in the years to follow (chapter 7). This is in line with the study of Nevins et al, that found that early declining medication nonadherence in the first two months was associated with adverse clinical outcomes, such as rejection and graft loss in the following 5-8 years (24). A study by Vlaminck et al found an association between non-adherence 1 year after transplantation and an increased risk for late acute rejection in the next 5 years (25). We demonstrated that patients who are already nonadherent at such a short time after kidney transplantation have worse clinical outcomes after kidney transplantation (4, 24). Therefore, maximizing medication adherence is a target for care to improve the long-term transplant outcomes.

Nonadherence in our studies was substantial and was related to poorer clinical outcomes, however, we do not know the extent to which our findings are generalizable to those who did not participate. In order to avoid participant-bias, we did not mention to the patient that our aim was to investigate nonadherence, but that we wanted to know about their attitudes towards and beliefs about the medication regime and how kidney disease and transplantation fitted into their lives. We do not know if patients are more or less adherent in the group of non-responders. For logistical reasons, we excluded patients who did not speak or understand Dutch. Maybe these patients are at even higher risk of being nonadherent. There is some evidence that patients with racial/ethnic differences in demographics are less adherent (26, 27). In elderly patients we included a group of 65 years and older who were fit enough to receive a kidney transplantation, these were therefore already survivors and thus a select group (28-30). Patients who were in nursing homes, had cognitive limitations, or were on dialysis were not included.

Attitudes and beliefs towards the medication regime

In this thesis attitudes were explored in kidney transplant recipients of different ages: young adults, the elderly, and in a group of all ages. The reason we wanted to explore attitudes of particularly younger and older patients was because nonadherence was believed to be associated with younger age (31-34). Moreover, there was little research on elderly kidney transplant patients who might experience difficulties due to deteriorating cognitive functions. In general, there is limited research on psychosocial factors associated with nonadherence among kidney transplant patients (21, 35). This was the first time that Q-methodology was used to investigate attitudes towards the medication regime after kidney transplantation. Q-methodology is a mixed method and combines the strength of qualitative and quantitative research, and is regarded a more robust technique than alternative (mixed) methods for the measurement of attitudes (36-40).

There were some similarities in attitude profiles found in the various studies, and some differences. With Q-methodology we were able to categorize young adult kidney transplant patients in 4 distinct attitude profiles (chapter 2). One attitude profile was suggested to be at risk of being nonadherent, namely 'easy going & pliable'. This group of 'easy going and pliable' young adults finds it more important to live their life to the fullest than to be adherent. Massey et al. found a high level of nonadherence (64.5%) in a group of young adult transplant recipients similar in age to the participants in chapter 2 (18). While adolescence and young adulthood are often associated with more nonadherence, we also found a profile in young adults that was very adherent and precise. This indicates that age is not always indicative of nonadherence and it is important to explore attitudes.

In addition, elderly patients could be categorized into two attitude profiles (chapter 4). One group labelled 'satisfied & easy going' was focused on leading a normal and enjoyable life who were not fearful or worried about the consequences of not taking their medication correctly. While the other group labelled 'reserved & concerned' experienced more physical and psychological complaints and were more fearful of the consequences of not taking medication correctly. We did not find any differences in adherence between the patients in these two attitude profiles (chapter 4). While in young adults there was also a group that was fearful of the consequences of being nonadherent, this was suggested to translate into more adherence. Also we found fewer attitude profiles among elderly recipients, presumably missing the more experimental or appearance-focused attitudes that typify younger age. This could be due to the fact that the more experimental group of young adults is not represented in the elderly group, or in other words; the patients in the 'easy going & pliable' group who found it more important to live their life to the fullest than to be adherent may be less likely to survive.

In our prospective study (chapter 5,6,7) we found 3 attitude profiles. Patients in the 'Confident and accurate' group take medication very accurately and feel confident in doing so. The second profile 'Concerned and vigilant', is similar to the 'reserved & concerned' profile found in elderly, these patients find it reassuring to check their kidney function regularly, but this is more out of fear of graft loss, while in the 'Confident and accurate' profile patients also find it reassuring to check their function regularly but their motivation is to confirm that they are doing well. The third profile 'appearance oriented and assertive' was also found both in the prospective study in all ages and in the study with young adults (chapter 2). These patients do not want their lives to revolve around their disease and have difficulties with the (cosmetic) side effects of the medication.

In conclusion 3 attitude profiles were repeatedly found in kidney transplant patients. First, an attitude profile that is concerned and afraid of graft loss but appears to be taking medication as prescribed, second, an attitude profile that is confident and not worried about graft loss and wants to live a normal life, and third, an attitude profile that found appearance important and experience side-effects of the medication.

In addition to attitudes we also investigated patients' beliefs about medication and the transplant and how post-transplant lifestyle and medications fits into patients' daily lives. Adherence was an important goal for patients, and kidney transplantation a real life-event. Our cohort study among kidney transplant patients (chapter 5,6,7) shows that patients report high-perceived necessity of immunosuppressive medication and relatively lower concerns about the medication in the beginning after transplantation. Lennerling et al. also found that patients had a high necessity of immunosuppressive medication and low concerns (35). Because our work was prospective, we were able to see this changes over time; some changes appear functional while others may be less functional. In the first six months post-transplant, perceived necessity of immunosuppressive medication decreased and belief in one's ability to carry out the regime decreased (chapter 5). In the longer follow-up, up to 18 months post-transplant, perceived necessity for the immunosuppressive medication continued to decrease, although the perceived impact of transplantation and negative emotional reaction to this decreased over time (chapter 6).

Associations with nonadherence

We did not find an association between the attitude profiles and self-reported nonadherence; this was equally distributed over the profiles. Thus, we did not find evidence for relationship between attitudes and behavior. Attitude alone is not a predictive factor of nonadherent behavior of patients; this finding highlights the discrepancy between the *beliefs* regarding transplantation and medication on the one hand and medication taking *behavior* on the other. Similarly to Lennerling and Forsberg who found a high necessity of immunosuppressive treatment and a high adherence rate on the VAS scale of the BAASIS. They found a nonadherence rate of 36% when scoring the BAASIS as we did in our studies. (35). This shows that actual behavior can be different than what the beliefs and attitude of patients are. What we did find was an association between attitudes and intra-patient variability in the pharmacokinetics of Tacrolimus (chapter 7). High intra-patient variability, i.e. high variability in blood trough levels of Tacrolimus, could be the result of variable Tacrolimus intake. Patients with the attitude 'concerned & vigilant' had a high intra-patient variability, and the patients with attitude ' confident & accurate' had a low intra-patient variability. This also suggests discrepancy between beliefs and actual behavior of patients. However, intra-patient variability was not related to clinical consequences (graft survival) whereas self-reported nonadherence was. This might be due to the short time after transplantation, the fact that patients are not yet stable and are not always well adjusted to their medication. Moreover a high intra-patient variability can also have other causes than nonadherence (41, 42). Which can make the intrapatient-variability measurement less accurate for nonadherence.

We found that patients who believed their graft would last longer were more likely to be nonadherent 6 months after transplantation (chapter 5). Patients with an unrealistic expectation that their graft will last a lifetime may underestimate the importance of medication in maintaining graft functioning. And those who reported a decreasing personal goal importance to adherence were more likely to become nonadherent over time (chapter 6).

With regard to socio-demographic characteristics, we found an association between nonadherence and being in paid employment. Ortega et al. found patients working outside the home reported lower levels of global satisfaction and convenience. Patients who were satisfied with their treatment show better compliance with prescriptions and play an active role in their own care (43). In our studies we found evidence that the most common reason for being classified as nonadherent was timing, not taking of the medication. We speculate that patients who have a job have difficulties with timing of medication because of they forget, having difficulties taking medication when with colleagues, or due to a busy schedule.

Furthermore we found an association between nonadherence and younger age. This is a continue variable, so we do not have a cut-off point of what age patients are at risk. The literature suggests that younger age can be a risk factor for nonadherence (11). The same goes for patients who make a transition from children's hospital into the adult care (34, 44). We also found no relationship between nonadherence and perceived necessity for or concerns about medication. What we did find was an increase in nonadherence over time parallel to a decrease in perceived need for medication. However there was no significant relation between these two factors. In contrast Hugon et al. found in a prospective study in a population of solid organ transplant recipients that negative beliefs (concerns) towards medications were shown to be an independent risk factor of poor adherence. The stronger the belief that medicines in general are harmful and overprescribed, the less adherent patients are likely to be (21).

Practical/clinical implications

In this thesis we were not able to pinpoint one single factor that was consistently predictive of nonadherence. Nevertheless specific attitudes profiles were (repetitively) found that give a unique insight into patient's perspectives on their medication regime. We now know the preferences of the patients with a certain attitude, and can as healthcare professionals interact with our patients according to their preferences and tailor the medical regime for them. The profiles can be used in clinical practice by making a short description of each of the profiles and asking the patient which profile they identified the most with (an example can be found in the appendix). This can help health care providers in adapting their care. Similarly Dwarswaard et al. underlined, in a thematic synthesis about self-management

needs, that patients vary in the extent to which they want to be involved in medical decision making and that changing the traditional (hierarchical) professional-patient relationship into a collaborative partnership is key (45). Our findings indicate that patients in each attitude profile demand a specific approach. For example the 'appearance oriented and assertive' patients are likely to thrive from a collaborative partnership where shared decision-making is central. With the right information and knowing the pros and cons they can contribute to decision-making regarding choice of medication. In young adults we now know that some patients with attitude 'opinionated & independent' want to be confronted by healthcare professionals with their nonadherent behavior in order to boost their motivation for adherence again. In addition to using short descriptions of the Q-profiles, when necessary the Q-sorting of the statements can be used as an intervention to communicate with young adults. The sorting of the statements can stimulate the young adult to think about his/her preferences/priorities with regards to treatment. We found in Q-methodology a tool to speak to young adults about complex issues such as nonadherence. The same experience was shared in other studies (46, 47). On the other hand Q-methodology was time consuming with elderly and therefore not that suitable for intervention in clinical practice for that specific group.

Younger age was found to be a risk factor for nonadherence, but among young adults there can also be a difference in attitude and behavior. Healthcare professionals should always be extra alert for nonadherence if patients are younger; nevertheless this thesis showed that nonadherence is present among kidney transplant patients of all ages.

The maintenance and persistence of the regime is an important target for intervention. Vrijens et al. describes the different stages of nonadherence; initiation, implementation, and discontinuation, but also the persistence is important (48). In the beginning (initiation phase) the majority of patients are well motivated but this decreases over time, especially if patients have unrealistic beliefs about the survival of their graft. Patients who assigned less importance to the goal adherence were more likely to become nonadherent. Additionally, these cognitions changed over time: the importance of medication adherence as a personal goal and perceived ability to carry out this behavior successfully (self-efficacy) significantly decreased over time. Patients need to be motivated to take their immunosuppressive medication. Motivation for adherence should be discussed regularly after transplantation and not only in the first months after transplantation as our findings showing adherence is likely to deteriorate over time. Also motivated patients can be nonadherent due to other factors. My own clinical experience is that every patient who has ever experienced graft loss due to nonadherence has his or her regrets. Based on this thesis, healthcare providers are recommended to discuss not only the need for and taking of medication but also the attitude, beliefs, motivation and expectations for the future.

As nonadherence is not a one-time event but an ongoing process, addressing nonadherence with the patient should be part of the routine of a healthcare professional during a patient consultation. The BAASIS-interview is a relatively easy and brief way of addressing the issue nonadherence in the outpatient clinic. Important considerations are how the questions are asked and the relationship between patient and healthcare professional. In addition the BMQ could be used to screen patients for negative beliefs towards their immunosuppressive medications (21). With this instrument the healthcare provider gains an inside in the way patients thinks about the needs and concerns about the medication. This could help healthcare professionals to discuss this feelings with the patient about their regime. This could increase the shared-decision making on how the regime best fits into a patient's life with the best outcomes. It is important to involve patients in the management of their own disease if they able to do so, and to encourage adherence as a personal goal. Healthcare professionals should also be vigilant to correct unrealistic beliefs that the graft will last an entire lifetime, particularly amongst younger patients, and emphasize that they can optimise their graft survival by good medication adherence.
All the major items are summarized in the box below.

The major items for nurse practitioners concerning non adherence after kidney transplantation are:	
1.	Nonadherence should be considered in ALL patients;
2.	The most common form of nonadherence is the TIMING of medication;
3.	Nonadherence is pervasive IMMEDIATELY after transplantation, and increases over time;
4.	Discussing adherence with patients in the outpatient clinic should be part of ROUTINE care;
5.	The BAASIS-interview or questionnaire is a recommended tool to quickly and effectively MEASURE non-adherence;
6.	ATTITUDE towards medication adherence can differ from actual adherence BEHAVIOR;
7.	Adherence should be stimulated as an important personal GOAL;
8.	Be vigilant to correct UNREALISTC EXPECTATIONS that a kidney transplant will last a lifetime;
9.	The sorting of the Q-statements can be used as an intervention to COMMUNICATE with uncommunicative young adults;
10.	Short descriptions of the Q-profiles can be used to explore ATTITUDES towards the regime.

Future directions

Our research showed early and increasing nonadherence after kidney transplantation. One third of kidney transplant patients are not always adherent to the medication regime. Patients have to take lifelong immunosuppressive drugs to prevent rejection of the graft and adhere to lifestyle changes. Future research should focus on two things. First, continuing to look for factors associated with adherence as targets for interventions. Not all determinants of nonadherence are known yet, so we are not able to identify specific groups of patients at risk for nonadherence. We need more follow-up time after transplantation to see if certain profiles are at risk for poorer clinical outcomes. Also we need to focus on other

dimensions than patient-related and therapy-related factors (10). We should also address health system/health care team factors and critically assess if multidisciplinary teams are involved in addressing nonadherence. Other factors to be investigated are the influence of the interaction between healthcare professionals and patients on adherence. Furthermore, are healthcare professionals such as nurse practitioners/doctors well trained enough to address the subject nonadherence. In a qualitative study by Been et al. nurses had divergent perceptions about self-management and their actual role in promoting this. Sufficient tools and training could help nurses operationalize self-management support in their daily working routine (49). More evidence is needed what kind of tools and training nurses can use to best contribute to the problem of nonadherence and self-management support in general.

Secondly, we have to develop interventions in the clinic to promote adherence. Interventions that help patients find a way to cope with their disease and adhere to the medication and lifestyle changes that comes with a kidney transplant. Interventions on improving adherence after kidney transplantation are scarce (50-52). Effective interventions are even more scarce. Nonadherence is present amongst the different groups of kidney transplant patients, this makes it hard to make an intervention that applies to the whole group of (non)adherent patients. An intervention should be tailored to the individual patient preferences. In a review about interventions for enhancing adherence in HIV patients, the authors found few interventions that successfully improved both adherence and clinical outcomes, with annotation that interventions based on theory of behavior would stand a better chance of improving adherence, but they found no evidence to support this (53). Motivational interviewing is one potential tool that could be used to promote importance of adherence as a personal goal (54, 55). Exploring and helping maintain high motivation for medication adherence may help prevent deteriorating adherence over time. Especially nurse practitioners are trained for balancing care and cure and can play an important role in adherence promotion (56). Therefore nurse practitioners may be a good choice as interventionists. Effective nurse-led interventions to enhance adherence are essential in order to achieve the best long-term clinical outcomes including quality of life after kidney transplantation.

References

1. Dew M, DiMartini A, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, et al. Rates and Risk Factors for Nonadherence to the Medical Regimen After Adult Solid Organ Transplantation. Transplantation. 2007;83(7):858-73.
2. Denhaerynck K, Steiger J, Bock A, Schäfer-Keller P, Köfer S, Thannberger N, et al. Prevalence and Risk Factors of Non-Adherence with Immunosuppressive Medication in Kidney Transplant Patients. American Journal of Transplantation. 2007;7(1):108-16.
3. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation. 2004;77(5):769-76.
4. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int. 2001 Oct;60(4):1565-70.
5. Loghman-Adham M. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. Am J Manag Care. 2003;9(2):155-71.
6. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA. 2002 Jul 24-31;288(4):455-61.
7. Osterberg L, Blaschke T. Adherence to Medication. New England Journal of Medicine. 2005;353(5):487-97.
8. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001 Aug;23(8):1296-310.
9. Denhaerynck K, Schmid-Mohler G, Kiss A, Steiger J, Wuthrich RP, Bock A, et al. Differences in Medication Adherence between Living and Deceased Donor Kidney Transplant Patients. Int J Organ Transplant Med. 2014;5(1):7-14.
10. WHO. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization2003.
11. Denhaerynck K, Dobbels F, Cleemput I, Desmyttere A, Schäfer-Keller P, Schaub S, et al. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. Transpl Int. 2005;18(10):1121-33.
12. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatric transplantation. 2005;9(3):381.
13. Rabe-Jablonska J, Bienkiewicz W. Anxiety disorders in the fourth edition of the classification of mental disorders prepared by the American Psychiatric Association: diagnostic and statistical manual of mental disorders (DMS-IV -- options book]. Psychiatr Pol. 1994 Mar-Apr;28(2):255-68.
14. Shemesh E, Lurie S, Stuber ML, Emre S, Patel Y, Vohra P, et al. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. Pediatrics. 2000 Feb;105(2):E29.
15. McCormick King ML, Mee LL, Gutierrez-Colina AM, Eaton CK, Lee JL, Blount RL. Emotional functioning, barriers, and medication adherence in pediatric transplant recipients. J Pediatr Psychol. 2014 Apr;39(3):283-93.
16. Chilcot J, Spencer BW, Maple H, Mamode N. Depression and kidney transplantation. Transplantation. 2014 Apr 15;97(7):717-21.
17. Cukor D, Newville H, Jindal R. Depression and immunosuppressive medication adherence in kidney transplant patients. Gen Hosp Psychiatry. 2008 Jul-Aug;30(4):386-7.
18. Massey EK, Meys K, Kerner R, Weimar W, Roodnat J, Cransberg K. Young Adult Kidney Transplant Recipients: Nonadherent and Happy. Transplantation. 2015 Feb 20.
19. Griva K, Davenport A, Harrison M, Newman SP. Non-adherence to immunosuppressive medications in kidney transplantation: intent vs. forgetfulness and clinical markers of medication intake. Ann Behav Med. 2012 Aug;44(1):85-93.

20. Weng FL, Chandwani S, Kurtyka KM, Zacker C, Chisholm-Burns MA, Demissie K. Prevalence and correlates of medication non-adherence among kidney transplant recipients more than 6 months post-transplant: a cross-sectional study. BMC Nephrol. 2013;14:261.
21. Hugon A, Roustit M, Lehmann A, Saint-Raymond C, Borrel E, Hilleret MN, et al. Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. Transplantation. 2014 Jul 27;98(2):222-8.
22. Cleemput I, Kesteloot K, Vanrenterghem Y, Sabina De G. The Economic Implications of Non-Adherence after Renal Transplantation. PharmacoEconomics. 2004;22(18):1217-34.
23. Chisholm-Burns MA, Spivey CA, Graff Zivin J, Lee JK, Sredzinski E, Tolley EA. Improving outcomes of renal transplant recipients with behavioral adherence contracts: a randomized controlled trial. Am J Transplant. 2013 Sep;13(9):2364-73.
24. Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. Transplantation. 2014 Oct 27;98(8):878-84.
25. Vlaminck H, Maes B, Evers G, Verbeke G, Lerut E, Van Damme B, et al. Prospective Study on Late Consequences of Subclinical Non-Compliance with Immunosuppressive Therapy in Renal Transplant Patients. Am J Transplant. 2004;4(9):1509-13.
26. Simoni JM, Huh D, Wilson IB, Shen J, Goggin K, Reynolds NR, et al. Racial/Ethnic disparities in ART adherence in the United States: findings from the MACH14 study. J Acquir Immune Defic Syndr. 2012 Aug 15;60(5):466-72.
27. Dickson VV, Knafl GJ, Riegel B. Predictors of medication nonadherence differ among black and white patients with heart failure. Res Nurs Health. 2015 Aug;38(4):289-300.
28. Orlandi PF, Cristelli MP, Aldworth CA, Freitas TV, Felipe CR, Silva Junior HT, et al. Long-term outcomes of elderly kidney transplant recipients. J Bras Nefrol. 2015 Apr-Jun;37(2):212-20.
29. Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant. 2007 Jul;22(7):1955-62.
30. Dimkovic N, Djukanovic L, Marinkovic J, Djuric Z, Knezevic V, Lazarevic T, et al. Achievement of guideline targets in elderly patients on hemodialysis: a multicenter study. Int Urol Nephrol. 2015 Jul 30.
31. Feinstein S, Keich R, Becker-Cohen R, Rinat C, Schwartz SB, Frishberg Y. Is Noncompliance Among Adolescent Renal Transplant Recipients Inevitable? Pediatrics. 2005;115(4):969-73.
32. Dew MA, Dabbs AD, Myaskovsky L, Shyu S, Shellmer DA, DiMartini AF, et al. Meta-Analysis of Medical Regimen Adherence Outcomes in Pediatric Solid Organ Transplantation. Transplantation. 2009;88(5):736-46.
33. Rianthavorn P, Ettenger RB. Medication non-adherence in the adolescent renal transplant recipient: a clinician's viewpoint. Pediatr Transplant. 2005 Jun;9(3):398-407.
34. Watson AR. Problems and pitfalls of transition from paediatric to adult renal care. Pediatr Nephrol. 2005 Feb;20(2):113-7.
35. Lennerling A, Forsberg A. Self-Reported Non-Adherence and Beliefs About Medication in a Swedish Kidney Transplant Population. The Open Nursing Journal. 2012;6:6.
36. Brown S. A primer on Q-methodology. Operant Subjectivity. 1993;16:91-138.
37. Brown S. Q-methodology and qualitative research. Qualitative Health Research. 1996;6(4):561-7.
38. Exel van N, De Graaf G. Q-methodology: A sneak preview2005: Available from: www.qmethod.org or www.rz.unibw-muenchen.de/p41bsmk/qmethod.
39. Cross RM. Exploring attitudes: the case for Q methodology. Health Educ Res. 2005;20(2):206-13.
40. Watts S, Stenner P. Doing Q Methodological Research. London: Sage Publications Ltd; 2012.
41. Shuker N, van Gelder T, Hesselink DA. Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. Transplant Rev (Orlando). 2015 Apr;29(2):78-84.

42. Shemesh E, Fine RN. Is calculating the standard deviation of tacrolimus blood levels the new gold standard for evaluating non-adherence to medications in transplant recipients? Pediatr Transplant. 2010 Dec;14(8):940-3.

43. Ortega F, Otero A, Crespo JF, Delgado JF, Borro JM, Cuervo J, et al. Satisfaction and adherence with immunosuppressant treatment in renal transplant patients living with a working graft. J Nephrol. 2013 Mar-Apr;26(2):297-305.

44. Watson AR. Non-compliance and transfer from paediatric to adult transplant unit. Pediatr Nephrol. 2000 Jun;14(6):469-72.

45. Dwarswaard J, Bakker EJ, van Staa A, Boeije HR. Self-management support from the perspective of patients with a chronic condition: a thematic synthesis of qualitative studies. Health Expect. 2015 Jan 26.

46. Jedeloo S, van Staa A, Latour JM, van Exel NJ. Preferences for health care and self-management among Dutch adolescents with chronic conditions: a Q-methodological investigation. Int J Nurs Stud. 2010 May;47(5):593-603.

47. van Exel NJ, de Graaf G, Brouwer WB. "Everyone dies, so you might as well have fun!" Attitudes of Dutch youths about their health lifestyle. Soc Sci Med. 2006 Nov;63(10):2628-39.

48. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012 May;73(5):691-705.

49. Been-Dahmen JM, Dwarswaard J, Hazes JM, van Staa A, Ista E. Nurses' views on patient self-management: a qualitative study. J Adv Nurs. 2015 Sep 11.

50. De Bleser L, Matteson M, Dobbels F, Russell C, De Geest S. Interventions to improve medication-adherence after transplantation: a systematic review. Transplant International. 2009;22(8):780-97.

51. Berben L, Denhaerynck K, Dobbels F, Engberg S, Vanhaecke J, Crespo-Leiro MG, et al. Building research initiative group: chronic illness management and adherence in transplantation (BRIGHT) study: study protocol. J Adv Nurs. 2015 Mar;71(3):642-54.

52. Low JK, Williams A, Manias E, Crawford K. Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review. Nephrol Dial Transplant. 2015 May;30(5):752-61.

53. Mbuagbaw L, Sivaramalingam B, Navarro T, Hobson N, Keepanasseril A, Wilczynski NJ, et al. Interventions for Enhancing Adherence to Antiretroviral Therapy (ART): A Systematic Review of High Quality Studies. AIDS Patient Care STDS. 2015 May;29(5):248-66.

54. Williams A, Manias E, Walker R, Gorelik A. A multifactorial intervention to improve blood pressure control in co-existing diabetes and kidney disease: a feasibility randomized controlled trial. J Adv Nurs. 2012 Nov;68(11):2515-25.

55. Garcia-Llana H, Remor E, del Peso G, Celadilla O, Selgas R. Motivational interviewing promotes adherence and improves wellbeing in pre-dialysis patients with advanced chronic kidney disease. J Clin Psychol Med Settings. 2014 Mar;21(1):103-15.

56. Peeters MJ, van Zuilen AD, van den Brand JA, Bots ML, van Buren M, Ten Dam MA, et al. Nurse practitioner care improves renal outcome in patients with CKD. J Am Soc Nephrol. 2014 Feb;25(2):390-8.

9

Summary

Nederlandse samenvatting

Summary

Patients with end stage renal disease (ESRD) benefit from kidney transplantation as the best renal replacement therapy. Kidney transplantation is the best option due to the advantages for patient survival and quality of life. There are two choices in renal transplantation; a living donor kidney transplantation (LDKT) or a deceased donor kidney transplantation (DDKT). A LDKT is the most favourable, because of the advantages for graft and patient survival. Patients have to take immunosuppressive medication after kidney transplantation to prevent rejection of the graft. According to the World Health Organization (WHO) adherence is defined as "the extent to which a person's behavior corresponds with the agreed recommendations from a health care provider". This thesis investigated patients' adherence behavior and attitudes and beliefs about the immunosuppressive regime.

Chapter 1 gives a general introduction about what kind of therapy and lifestyle is required after kidney transplantation. Patients have to be adherent to their immunosuppressive medication regime. This most commonly consists of two intake moments of medicine a day, although patients are likely to have other additional medication for other comorbidities making this regime even more complex. There are five interacting dimensions that affect adherence according to the world health organization (WHO). The first is 'social and economic factors', for example poverty, race, age, and insurance. The second dimension is 'the health care team and system-related factors', such as patient-provider relationship. The third dimension 'condition-related factors' is the severity of symptoms or disease and how they influence patients' perception of risk if they deviate from the prescribed regime. The fourth dimension is 'therapy-related factors' like the complexity of the medical regime and the side effects of that regime. The fifth and last dimension is 'patient-related factors' which represents the resources, knowledge, attitudes, beliefs, perceptions, and expectations of the patient.

This chapter also describes nonadherence among kidney transplant patients and how this is monitored. Furthermore there are many factors that can have an influence on the graft survival; nonadherence is a potential contributing factor.

At the end of this chapter the aim of this thesis and specific research question are presented. The aim of the thesis was to gain a better understanding of (change in) immunosuppressive medication nonadherence and in particular the psychosocial aspects of behavior after kidney transplantation in order to inform the care that nurse practitioners can offer in the clinic. The research questions in this thesis were: (1) What is the rate of nonadherence among our population of kidney transplant recipients and does this change over time? (2) What are the attitudes, beliefs and goals of kidney transplant recipients towards the medication regime? (3) To what extent are these attitudes, beliefs and goals related to nonadherence? (4) To what extent is nonadherence related to graft survival?

Chapter 2 describes a cross sectional study on attitudes toward s the medication regime among young kidney transplant patients. A Q-methodological (mixed-methods) study was conducted among 26 young adults (18-25 years). Four distinct attitude profiles concerning post-transplant health lifestyle were found: (i) concerned & controlled, (ii) appearance orientated, (iii) opinionated & independent, and (iv) easy going & pliable. (For the four short descriptives see appendix).

The young adults loading on the first factor (i) 'concerned & controlled' worry that their kidney will be rejected and are concerned about their future. They are careful about their medication and their health behavior, and find it more important to be adherent than to have a good life now. Non-adherence leads to feelings of guilt. Young adults loading on the second factor (ii) are 'appearance-orientated', do not wish their life to revolve around their disease, and believe that after transplantation they can live a normal life. The risk for non-adherence seems relatively small in these young adults, but the fear for cosmetic side-effects of immunosuppressant's, and the tendency to be uncommunicative about their transplant in their social environment, may interfere with adherence. Young adults loading on the third factor (iii) 'opinionated & independent' believe strongly about not wanting to go back on dialysis again and do not wish their life to revolve around their disease. They seek a normal life, with the least possible limitations from their regime. More than in other groups, these young adults are scared of a rejection because of nonadherence. Young adults loading on the fourth factor (iv) 'easy going & pliable' find it more important to live a good life now than to be compliant and think nothing bad will happen if they forget their medication. These young adults seems to be uninformed or uninterested in their illness and regime, and not to foresee or accept the risks of their nonadherent behavior. We speculate therefore that their risk of nonadherence is high. Thirty-four young adult transplant recipients were subsequently asked to what extent they identified themselves with these 4 profiles. Self-categorization on these attitudes seems feasible and may be a useful screening aid to identify young adults at risk of non-adherence.

Chapter 3 describes the results of the Q-methodology in-depth interview study in Chapter 1 focusing on the four statements related to the medication regime. Statement 1; "If you forget your medication, nothing really bad will happen". Statement 2; "I never forget my medication". Statement 3; "When I stay in bed late, I just take my medication later", and statement 4; "When I am out with friends, I am not very punctual with medication". Ten of the 26 patients felt that forgetting medication would not lead to serious consequences. They had developed all kind of theories about why there would be no serious consequences. Half of the respondents (48%) stated that they never forget their medication. Most young adults (80%) have no problems with taking medication when with friends. Remarkably, 72% of the young adults admitted not always taking their medication on time. After going out with friends the day before, they forget to take their medication on the prescribed time.

Especially during the weekend young adults experience problems with the regular intake of immunosuppressive medication. Apparently, young adults are not too accurate with the medication, especially when it does not fit in with their life style and with important social activities such as going out with friends. This study is very relevant for healthcare professionals because it helps to understand the motivation behind nonadherence behavior among young adult transplant recipients.

Chapter 4 describes a study that investigated attitudes towards the post-transplant regime of immunosuppressive medication among the elderly kidney transplant recipients (>65 years). Two distinct attitudes were found: 'satisfied & easy going' and 'reserved & concerned'. Satisfied and easy-going patients focus on leading a normal and enjoyable life and are not fearful or worried about the consequences of not taking their medication correctly. Reserved and concerned elderly patients experience more psychical and psychological complaints are more fearful of consequences of not taking their medication correctly. These attitudes imply different needs for assistance, monitoring and risk of nonadherence. The proportion of elderly that forgets their medication is considerable, but not different between the two attitude profiles.

Chapter 5 describes a prospective cohort study where we investigated whether changes in goal cognitions, illness perceptions, and treatment beliefs were related to self-reported medication adherence six months after kidney transplantation. The cohort consisted of 113 kidney transplant patients at baseline 6 weeks after transplantation. We found that self-reported nonadherence increased significantly between 6 weeks and 6 months after transplantation from 17% to 27%. Importance of medication adherence as a personal goal and self-efficacy to successfully carry out this goal was high but decreased significantly over time. Perceived necessity of immunosuppressive medication was also high but significantly decreased over time. Concerns about the medicines were low. There were no significant changes in illness perceptions or concerns over time. An increase in perceived graft longevity (timeline) was related to higher likelihood of nonadherence six months post-transplant. Furthermore, younger adult patients were more likely to be nonadherent six months after transplantation. The self-reported nonadherence levels found in this study so soon after transplantation demonstrate the need for early and continued intervention after kidney transplantation in order to maximize adherence. Changes in (unrealistic) beliefs regarding the longevity of the graft may offer a potential target for intervention among nonadherent patients.

Chapter 6 describes the 18-month follow-up of the prospective cohort study presented in chapter 5. Here we see nonadherence significantly increased from 17% at 6 weeks to 31% at 18 months after transplantation. Perceived necessity of medication, perceived impact of transplant on life (consequences) and emotional response to transplantation significantly decreased over time. Participants who reported low importance of medication adherence

as a personal goal were more likely to become nonadherent over time. Illness perceptions can be described as functional and supportive of adherence, which is inconsistent with the pervasive and increasing nonadherence observed. There appears therefore to be a discrepancy between beliefs about adherence and actual behavior. Promoting (intrinsic) motivation for adherence goals and exploring the relative importance in comparison to other personal goals is a potential target for interventions.

Chapter 7 describes attitudes towards medication adherence 6 weeks after transplantation using Q-methodology in the same cohort described in chapters 5 and 6. The three attitudes found were 1; "Confident & Accurate", 2; "Concerned & Vigilant", and 3; "Appearance oriented & Assertive". Patients with the attitude 'Confident & Accurate' were confident about managing their medication regime 6 weeks after transplantation and had significantly lower variability of tacrolimus in their blood. Patients with the attitude 'Concerned & Vigilant' reported anxiety about the medication and nonadherence and were significantly related to higher variability of tacrolimus in the blood compared to the 'confident & accurate' patients. These findings suggest that individuals characterized by anxiety about their medication regime may be less adherent or, alternatively, that patients who have more problems with their medication are more worried. This association between attitude and adherence was, however, only found when adherence was measured using levels of medication found in the blood, not when using self-report. Patients with attitude 'Appearance oriented & Assertive' want to live a normal life, be in control and think they are capable of taking care of their kidney, but also experience side effects. Although their intra-patient variability of tacrolimus was not elevated, we speculate that these patients may have a higher risk of nonadherence in the future because they are concerned about (cosmetic) side effects of their medication regimen.

The Q-methodology study thus uncovered different attitudes towards medication adherence that requires different approaches from healthcare professionals. We found an association between attitudes and intra-patient variability in pharmacokinetics of tacrolimus, but not with self-reported nonadherence or graft survival and with clinical endpoints such as graft rejection or graft survival. In contrast, self-reported nonadherence 6 weeks after transplantation was associated with graft failure in the subsequent 2-year period. These findings suggest that nonadherence shortly after kidney transplantation may be a risk factor for lower graft survival in the years to follow. The attitudes towards medication were not related to adherence behavior, but nurses experienced the interview method used as helpful to interact with patients about this difficult clinical topic. These results will inform the development and tailoring of self management programmes for patients shortly after transplantation.

Chapter 8 describes the general discussion and gives an integration of all the study results. With the following major items for nurse practitioners regarding non-adherence.

The major items for nurse practitioners concerning non adherence after kidney transplantation are:	
1.	Nonadherence should be considered in ALL patients;
2.	The most common form of nonadherence is the TIMING of medication;
3.	Nonadherence is pervasive IMMEDIATELY after transplantation, and increases over time;
4.	Discussing adherence with patients in the outpatient clinic should be part of ROUTINE care;
5.	The BAASIS-interview or questionnaire is a recommended tool to quickly and effectively MEASURE non-adherence;
6.	ATTITUDE towards medication adherence can differ from actual adherence BEHAVIOR;
7.	Adherence should be stimulated as an important personal GOAL;
8.	Be vigilant to correct UNREALISTC EXPECTATIONS that a kidney transplant will last a lifetime;
9.	The sorting of the Q-statements can be used as an intervention to COMMUNICATE with uncommunicative young adults;
10.	Short descriptions of the Q-profiles can be used to explore ATTITUDES towards the regime.

Nederlandse samenvatting

Voor patiënten met eindstadium nierfalen is niertransplantatie de beste nierfunctie vervangende therapie. Niertransplantatie is de beste optie omdat het de beste kwaliteit van leven geeft ten opzichte van de andere nierfunctie vervangende therapieën en zorgt voor de beste patiënten overleving. Er zijn twee verschillende vormen van niertransplantatie: een levende donornier transplantatie of een postmortale donornier transplantatie. Een levende donornier transplantatie heeft de voorkeur, vanwege de voordelen voor het transplantaat (nier) en de overleving van de patiënt. Patiënten dienen na een niertransplantatie immunosuppressiva in te nemen om afstoting van de donornier te voorkomen. Volgens de World Health Organization (WHO) is de definitie van therapietrouw: "de mate waarin iemands gedrag correspondeert met de overeengekomen aanbevelingen van een zorgverlener". Dit proefschrift onderzocht de houding en overtuigingen van patiënten ten opzichte van hun medicatie regime en therapietrouw gedrag na niertransplantatie.

Hoofdstuk 1 geeft een inleiding over wat voor therapie en levensstijl nodig is na een niertransplantatie. Patiënten moeten zich houden aan de medicatie voorschriften van de immunosuppressiva. Deze immunosuppressiva dient normaliter op twee momenten per dag te worden ingenomen, maar deze patiënten hebben vaak nog meer medicatie ten gevolge van co morbiditeit en dat maakt het medicatieregime nog complexer. Therapieontrouw heeft een negatieve invloed op de niertransplantaatoverleving op de lange termijn. Volgens de World Health Organization (WHO) zijn er 5 interactieve dimensies die de therapietrouw kunnen beïnvloeden. De eerste zijn 'sociale en economische factoren', denk aan armoede, etniciteit, leeftijd en zorgverzekering. De tweede dimensie is 'het gezondheidszorg team en systeem gerelateerde factoren', zoals de behandelrelatie tussen de patiënt en zorgverlener. De derde dimensie 'conditie gerelateerde factoren' is de ernst van de symptomen van de ziekte en welk risico patiënten nemen als ze afwijken van het voorgeschreven regime. De vierde dimensie is 'therapie gerelateerde factoren' zoals de complexiteit van het medicatieregime en de bijwerkingen van de medicatie. De vijfde en laatste dimensie is 'patiënt gerelateerde factoren' wat de kennis, houding, overtuiging en verwachtingen van een patiënt vertegenwoordigd. In dit hoofdstuk wordt ook therapieontrouw onder niertransplantatie patiënten beschreven en de diverse methoden om dit te meten. Verder zijn er veel factoren die invloed kunnen hebben op de transplantaatoverleving waaronder therapieontrouw.

Het doel van dit proefschrift was om inzicht te krijgen over (veranderingen in) therapieontrouw en voornamelijk meer inzicht in de psychosociale factoren die van invloed zouden kunnen zijn op therapieontrouw gedrag. Zodat verpleegkundig specialisten de poliklinische zorg voor patiënten kunnen verbeteren.

De onderzoeksvragen van dit proefschrift waren: (1) Hoe vaak komt therapieontrouw voor onder onze populatie niertransplantatiepatiënten en verandert dit over de tijd? (2) Wat zijn de houdingen, overtuigingen en doelen van een niertransplantatiepatiënt ten opzichte van zijn medicatie regime? (3) Zijn houdingen, overtuigingen en doelen van patiënten van invloed op de therapieontrouw? (4) Is therapieontrouw van invloed op de niertransplantaatoverleving?

Hoofdstuk 2 beschrijft een crossectionele studie over houdingen ten aanzien van de medicatie onder jong volwassen niertransplantatiepatiënten. Deze Q-methodologische (gecombineerde methode kwalitatief/kwantitatief) studie werd verricht onder 26 jong volwassenen (18-25 jaar). Vier afzonderlijke factoren van houdingen ten opzichte van het medicatie regime en het leven na een niertransplantatie werden gevonden: (i) bezorgd & gecontroleerd, (ii) uiterlijk georiënteerd & gesloten, (iii) relaxed, eigenwijs & zelfstandig, en (iv) makkelijk & meegaand. (Zie de bijlage voor 4 korte beschrijvingen). De jong volwassenen die op de eerste factor laden (i) 'bezorgd & gecontroleerd' zijn bezorgd dat de donornier zal afstoten en maken zich zorgen om hun toekomst. Ze zijn zorgvuldig met de medicatie en leven gezond, zij vinden het belangrijker om volgens de regels te leven dan nu te genieten. Therapieontrouw leidt tot schuldgevoelens. Jong volwassenen die laden op de tweede factor (ii) zijn 'uiterlijk georiënteerd & gesloten', zij willen niet dat hun leven om de ziekte draait, zij geloven dat ze na een niertransplantatie gewoon een normaal leven kunnen leiden. Het risico op therapieontrouw bij deze jong volwassenen lijkt redelijk klein, maar de angst voor cosmetische bijwerkingen van de immunosuppressiva en de neiging om gesloten te zijn over hun niertransplantatie in hun sociale omgeving zal mogelijk invloed kunnen hebben op de therapietrouw. Jong volwassenen die laden op de derde factor (iii) 'relaxed, eigenwijs & zelfstandig' willen absoluut niet (terug) naar de dialyse en willen ook niet dat hun leven om de ziekte draait. Zij willen een normaal leven en geen beperkingen ervaren ten aanzien van hun medicatie regime. Meer dan in de andere factoren zijn deze jong volwassenen bang voor afstoting als gevolg van therapieontrouw. Jong volwassenen die laden op de vierde factor (iv) 'makkelijk & meegaand' vinden het belangrijker om nu lekker te leven dan om therapietrouw te zijn. Zij denken dat er niks ergs gebeurt als je af en toe je medicijnen vergeet. Deze jong volwassenen lijken niet goed geïnformeerd of ongeïnteresseerd in hun aandoening te zijn en bijbehorende regime en lijken niet goed in staat om hun risico's te overzien of te accepteren na therapieontrouw gedrag. Wij speculeren dat het risico op therapieontrouw bij deze jongeren hoger zal zijn. 34 jong volwassen niertransplantatiepatiënten werden vervolgens gevraagd of zij zichzelf konden identificeren met deze 4 factoren. Zelf categorisatie op deze factoren lijkt uitvoerbaar en kan een nuttig instrument zijn om jongeren te identificeren voor een risico op therapieontrouw.

Hoofdstuk 3 beschrijft de resultaten van de diepte-interviews van de Q-methodologie studie in hoofdstuk 1 gericht op de 4 stellingen die direct gerelateerd waren aan het

medicatie regime. Stelling 1; “Als je een paar keer je medicijnen vergeet, zal er echt niets gebeuren”. Stelling 2; “Ik vergeet mijn medicijnen eigenlijk nooit”. Stelling 3; “Als ik uitslaap, neem ik mijn medicijnen gewoon wat later in”, en stelling 4; “Als ik met vrienden ga stappen of op vakantie ben, neem ik het niet zo nauw met mijn medicijnen”. Tien van de 26 patiënten dachten dat het vergeten van medicatie geen consequenties zou hebben. Ze hadden diverse theorieën ontwikkeld waarom dat geen serieuze consequenties kon hebben. De helft van de respondenten (48%) verklaarden dat zij nooit hun medicatie vergaten. De meerderheid van de jong volwassenen (80%) had geen moeite met het innemen van medicatie in het bijzijn van vrienden. Opmerkelijk was dat 72% van de jong volwassenen toegaven dat ze hun medicatie niet altijd op de voorgeschreven tijd innamen, vooral als ze de dag daarvoor met vrienden waren uit geweest. Vooral tijdens het weekend ervaren jong volwassenen problemen met het op tijd innemen van de immunosuppressiva. Blijkbaar zijn jong volwassenen niet altijd even accuraat met de voorgeschreven medicatie, vooral als het niet in hun levensstijl past en interfereert met belangrijke sociale activiteiten zoals uitgaan met vrienden. Deze studie is van belang voor zorgverleners omdat het inzicht geeft over de motivatie achter therapieontrouw gedrag van jong volwassen niertransplantatiepatiënten.

Hoofdstuk 4 beschrijft een studie over houdingen ten aanzien van het medicatie regime van immunosuppressiva onder de oudere niertransplantatiepatiënten (>65 jaar). Twee onderscheidende houdingen werden gevonden: ‘tevreden & ontspannen’ en ‘gereserveerd & bezorgd’. Tevreden en ontspannen patiënten richten zich op een normaal en plezierig leven en zijn niet angstig of bezorgd over de consequenties als ze de medicatie niet goed innemen. Gereserveerde en bezorgde oudere patiënten ervaren meer psychische en psychologische klachten en zijn angstiger voor de consequenties als ze de medicatie niet goed innemen. Deze houdingen impliceren verschillende behoeftes voor begeleiding, bejegening en risico op therapieontrouw bij oudere patiënten. De hoeveelheid ouderen die de medicatie vergeet is aanzienlijk, maar niet verschillend tussen de twee verschillende houdingen.

Hoofdstuk 5 beschrijft een prospectieve cohort studie waar we onderzochten of veranderingen in doel en, ziektepercepties, en overtuigingen ten aanzien van de behandeling van invloed waren op zelf-gerapporteerde medicatie therapieontrouw 6 maanden na niertransplantatie. Aan het beginpunt, 6 weken na niertransplantatie, bestond het cohort uit 113 niertransplantatiepatiënten. Zelf-gerapporteerde therapieontrouw nam significant toe tussen 6 weken en 6 maanden na transplantatie van 17% tot 27%. Het belang van therapietrouw als een persoonlijk doel en zelfredzaamheid om zelfstandig dit doel uit te voeren was hoog maar dit nam significant af in de loop van de tijd. De ervaren noodzaak van immunosuppressiva was hoog maar ook dit daalde significant in de loop der tijd. Zorgen over de medicatie waren laag. Er waren geen significante veranderingen in ziektepercepties of zorgen over transplantatie over de tijd. Een toename in verwachte levensduur van het niertransplantaat door de patiënt is gerelateerd aan een hogere kans op therapieontrouw zes maanden na niertransplantatie.

Verder hadden jongere volwassenen meer kans op therapieontrouw 6 maanden na niertransplantatie. In deze studie laat de mate van zelf-gerapporteerde therapieontrouw zo vroeg na niertransplantatie een noodzaak zien voor een vroege en continue interventie om de therapietrouw te verbeteren. Veranderingen in (onrealistische) overtuigingen ten opzichte van de verwachte levensduur van het transplantaat kan een belangrijk doel voor interventie zijn onder therapieontrouwe patiënten.

Hoofdstuk 6 beschrijft de 18 maanden follow-up van het cohort van de prospectieve studie zoals beschreven in hoofdstuk 5. Hier zien we dat de therapieontrouw significant toeneemt van 17% op 6 weken tot 31% op 18 maanden na transplantatie. De ervaren noodzaak voor de medicatie, waargenomen effect van het transplantaat op het leven (consequenties) en de emotionele reactie op de transplantatie daalde significant over de tijd. Deelnemers die therapietrouw niet als persoonlijk doel beschouwen hadden meer kans om therapieontrouw te worden over de tijd. Ziekte percepties kan beschreven worden als functioneel en bevorderend voor therapietrouw, wat inconsequent is met de alomtegenwoordige en toenemende therapieontrouw die is waargenomen. Er lijkt een discrepantie te bestaan tussen overtuigingen over therapietrouw en werkelijk gedrag. Bevordering van (intrinsieke) motivatie voor naleving van de doelstellingen en het verkennen van het relatieve belang in vergelijking met andere persoonlijke doelen zijn potentiele doelwitten voor interventies.

Hoofdstuk 7 beschrijft houdingen ten aanzien van de naleving van de medicatie 6 weken na de transplantatie met behulp van Q-methodologie in dezelfde cohort beschreven in de hoofdstukken 5 en 6. De drie houdingen die werden gevonden zijn, 1; “zelfverzekerd & precies”, 2; “bezorgd & waakzaam”, en 3; “uiterlijk georiënteerd & assertief”. Patiënten met de houding “zelfverzekerd & precies” waren zelfverzekerd over het regelen van hun medicatie regime 6 weken na transplantatie en hadden significant lagere variabiliteit van tacrolimus concentraties in hun bloed. Patiënten met de houding “bezorgd & waakzaam” rapporteerden angst over de medicatie en therapieontrouw en waren significant gerelateerd aan een hogere variabiliteit van tacrolimus concentraties in het bloed in vergelijking met de patiënten met houding “ zelfverzekerd & precies”. Deze bevindingen suggereren dat individuen gekenmerkt door angst over hun medicatie regime mogelijk minder therapietrouw zijn of, andersom beredeneerd, dat patiënten die meer problemen met hun medicatie hebben meer bezorgd zijn. Deze associatie tussen houding en therapietrouw is echter alleen gevonden wanneer therapietrouw werd gemeten met behulp van tacrolimusspiegels in het bloed, niet bij de zelf gerapporteerde therapieontrouw. Patiënten met de houding “uiterlijk georiënteerd & assertief” willen een normaal leven leiden, de regie houden en denken dat ze goed in staat zijn om voor hun transplantaatnier te zorgen, maar ervaren ook bijwerkingen. Hoewel hun intra-patiënten variabiliteit van tacrolimus niet gestegen was, zijn wij van mening dat deze patiënten mogelijk in de toekomst een hoger risico hebben op therapieontrouw omdat ze zich zorgen maken om de (cosmetische) bijwerkingen van het

medicatie regime. De Q-methodologie studie toont dus verschillende houdingen ten aanzien van de medicatie en therapie waarvoor verschillende benaderingen van beroepsbeoefenaren in de gezondheidszorg worden gevraagd. We vonden een samenhang van de houdingen van patiënten met intra-patiënten-variabiliteit in farmacokinetiek van tacrolimus. We vonden geen samenhang van houdingen van patiënten met zelf-gerapporteerde therapieontrouw of transplantaatoverleving en klinische eindpunten zoals afstoting of transplantaatoverleving. In tegenstelling tot zelf-gerapporteerde therapieontrouw 6 weken na transplantatie dat werd geassocieerd met transplantaatverlies in de daaropvolgende periode van 2 jaar. Deze bevindingen suggereren dat therapieontrouw kort na niertransplantatie een risicofactor kan zijn voor een lagere transplantaatoverleving in de jaren die volgen. De houdingen ten opzichte van het medicatie regime waren niet gerelateerd aan therapietrouw gedrag, maar verpleegkundigen ervaren de interview methode die wordt gebruikt als een nuttig instrument om te communiceren met patiënten over dit moeilijke klinische onderwerp. Deze resultaten worden gebruikt voor het verder informeren en ontwikkelen van een zelfmanagementprogramma voor patiënten kort na transplantatie.

Hoofdstuk 8 beschrijft de algemene discussie en geeft een integratie van alle studieresultaten. Onderstaand de belangrijkste aandachtspunten voor verpleegkundig specialisten samengevat.

Belangrijke aandachtspunten voor verpleegkundig specialisten met betrekking tot therapieontrouw na niertransplantatie	
1.	Bij ALLE patiënten dient men alert te zijn op therapieontrouw;
2.	Het niet innemen van medicatie op de voorgeschreven TIJD is de meest voorkomende vorm van therapieontrouw;
3.	Therapieontrouw kan DIRECT na transplantatie voorkomen en neemt toe in de loop van de tijd;
4.	Het bespreken van therapietrouw met patiënten in de polikliniek moet deel uitmaken van de STANDAARD zorg;
5.	De BAASIS-interview/vragenlijst is een aanbevolen hulpmiddel om snel en effectief therapieontrouw te METEN;
6.	HOUDING ten aanzien van therapietrouw kan verschillen van therapietrouw GEDRAG;
7.	Therapietrouw dient gestimuleerd te worden als een persoonlijk DOEL;
8.	Corrigeer patiënten die ONREALISTISCHE VERWACHTIGINGEN hebben over de levensduur van de donornier;
9.	Het rangschikken van de Q-stellingen kan worden gebruikt als een interventie om te COMMUNICEREN met ontoegankelijke jong volwassenen;
10.	Korte beschrijvingen van de Q-profielen kunnen worden gebruikt om inzicht te krijgen in de HOUDING van een patiënt ten aanzien van de therapie en de zorg daarop aan te passen.

Phd Portfolio

PhD Portfolio

1. Phd-training		year	hrs	ECTS
Seminars and workshops				
-7th Annual conference V&VN VS, Papendal; workshop statistics		2015	4	
-LWTV (Landelijke werkgroep transplantatie verpleegkundige) workshop, Wolfheze (including nonadherence)		2015	7	
International Presentations	**Presentation**			
-Ethical, Legal and Psychosocial Aspects of organ Transplantation, Rotterdam, The Netherlands	Oral	2013		1
-29th Annual Q Conference, Amsterdam, The Netherlands	Oral	2013		1
-28th Annual Q Conference, Pittsburgh, USA	Oral	2012		1
-The Transplantation Society, Berlin, Germany	Oral	2012		1
-European Society for Patient Adherence,COMpliance and Persistence, Utrecht, The Netherlands	Oral	2011		1
-International Transplant Nurses Society, Gothenburg, Sweden	Oral	2011		1
	Oral (2)	2010		2
-International Transplant Nurses Society; Minneapolis, USA	Oral	2009		1
-International Transplant Nurses Society; Montreal, USA	Poster	2009		1
-American Transplant Congress; Boston, USA	Poster	2007		1
-International Transplant Nurses Society; St Louis, USA	Oral	2007		1
-International Transplant Nurses Society; Denver, USA	Oral	2007		1
-American Transplant Congress; San Francisco, USA	Oral	2007		1
- Ethical, Legal and Psychosocial Aspects of organ Transplantation, Rotterdam, The Netherlands	Oral	2006		1
-International Transplant Nurses Society; Rotterdam, The Netherlands: workshop presenter	Poster	2005		1
-American Transplant Congress; Seattle, USA	Oral	2005		1
-European Society of Transplant, Geneva, Switzerland				
National Presentations	**Presentation**			
-7th Annual conference V&VN VS, Papendal	Oral	2015		1
-Annual conference NTV (bootcongres), Leiden	Laptop	2014		1
-5th Annual conference V&VN VS, Papendal	Oral	2013		1
-Annual conference NTV (bootcongres), Maastricht	Oral	2012		1
-Annual conference NTV (bootcongres), Rotterdam	Oral	2010		1
-Annual workshop Zeist; workshop presenter	Oral	2009		1
2. Teaching				
Lecturing				
-Lectures at meetings for patients		2006-2015	8	
-Lectures for professionals		2006-2015	12	
-Minor for students		2015		
Supervision				
-Supervision of masterthesis MANP student		2014	2	
-Nurse teacher of MANP student		2011-2013	8	

3. Other activities	
Professional memberships	
- ITNS (international transplant nurses society)	2008-2015
- LWTV (landelijke werkgroep transplantatie verpleegkundige)	2008-2015
-V&VN VS (Verpleegkundigen & Verzorgenden Nederland, platform Verpleegkundig Specialist)	2004-2015
Committee memberships	
-Board member of foundation OWVS (stichting ondersteuning wetenschappelijk onderzoek voor verpleegkundig specialisten)	2012-2015 2010-2015
-Secretary of the nurse practitioners Erasmus MC group	2008-2013
-Chair of the LWTV (landelijke werkgroep transplantatie verpleegkundige)	2004-2010
-Chair of the Nurse Practitioners Erasmus MC group	
Grants	
-Researchgrant; EBCN (Evidence Based Care for Nurses; €20.000)	2011
Awards	
-Best presentation NTV annual congress	2012

List of publications

List of publications

Tielen, M., J. van Exel, et al. (2014). “Attitudes to medication after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study.” J Transplant 2014: 675301.

Tielen, M., N. J. A. van Exel, et al. (2011). “Attitudes towards medication non-adherence in elderly kidney transplant patients: a Q methodology study.” Nephrol Dial Transplant 26(5): 1723-1728.

Tielen, M., A. L. van Staa, et al. (2008). “Q-Methodology to Identify Young Adult Renal Transplant Recipients at Risk for Nonadherence.” Transplantation 85(5): 700-706.

Tielen M, S. Jedeloo, A.L. van Staa, W. Weimar, (2008) “Immunosuppressive Drugs and Young Adults: A Difficult combination”, Organ Transplantation: Ethical, Legal and Psychosocial Aspects towards a Common European Policy*, W. Weimar, M.A. Bos, J.J. Busschbach, ISBN 978-3-89967-415-6, 2008, 563-569.*

Massey, E. K., M. Tielen, et al. (2015). “Discrepancies between beliefs and behavior: a prospective study into immunosuppressive medication adherence after kidney transplantation.” Transplantation 99(2): 375-380.

Grijpma J. W, Tielen M, et al. (2016). “Kidney transplant patients’ attitudes towards self-management support: A Q-methodological study”, Patient Educ Couns doi:10.1016/j.pec.2015.11.018.

Massey, E. K., M. Tielen, et al. (2013). “The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: A cohort study.” Journal of Psychosomatic Research 75(3): 229-234.

Curriculum vitae

Curriculum vitae

Mirjam Moors-Tielen was born on May 31, 1977 in Eindhoven, the Netherlands. After completing secondary school at Kempenpoort, Eindhoven in 1996, she qualified as a Registered Nurse in 2001 at the Hogeschool Rotterdam. She started working at the transplant unit of the University Medical Center of Rotterdam in 2001 as a RN. There she developed an interest in kidney transplantation and applied to the department to create a position as nurse practitioner in the field of kidney transplantation. The request was accepted in 2004 and Mirjam completed her Master in Advanced Nursing Practice in 2006. This was the first class of students to graduate with the MANP degree in Rotterdam. She is now a nurse practitioner with more than 10 years' experience in the field of kidney transplantation for adult patients at the Erasmus University Medical Center in Rotterdam. She has a special interest in immunosuppressive medication adherence and Q-methodology. She is an active member of several nursing organizations and was, for example, the President of the Dutch Workgroup of Transplant Nurses for 5 years. Currently, she is a board member of the nurse practitioner group in the Erasmus Medical Center and is also board member of the foundation of OWVS since 2013 (Ondersteuning Wetenschappelijk onderzoek Verpleegkundig Specialist). In her work as a nurse practitioner she works mainly at the outpatient clinic, evaluating transplant candidates and their living donors as well as providing post-transplant care. She lives in Breda with her husband Xavier Moors and their three children, Evi (2008), Dex (2012) and Cas (2014).

Q short descriptives

Short Q-descriptive used in young adult renal transplant patients
Which profile fits the most?

A

I am always worried that my kidney will reject. I think it is important to check my kidney function in the outpatient clinic regularly, so I make sure I'm doing all right. I worry about the future, how long will my graft survive. That kind of questions keep me occupied. I am sometimes gloomy. I take good care of myself and I am very sparingly with my kidney. In comparison with other people I'm tired more. I have side-effects of the medication. I can say no to friends. Sometimes I feel guilty when I eat too much. I hardly forget my medication and I am always on time with taking my pills.

Not at All | not | A little | good | Very good

☐ ☐ ☐ ☐ ☐

B

I think that the way I look is very important, and I don't like the scars after my kidney transplantation. It is frustrating that you gain weight after transplantation or can't lose it. I think I have side-effects of the medication. Nevertheless, I can do everything and live a normal life. Sometimes I am insecure whether I can find a relationship. I rather don't tell I have a kidney transplant. Sometimes it is hard to tell where my boundaries are, because I want to be normal. I hardly forget my medication. I think it is possible to do something that is not always the healthiest way.

Not at All | not | A little | good | Very good

☐ ☐ ☐ ☐ ☐

C

I never want to go back on dialyses, that was horrific. I hate living by too many rules. I am open about telling of my kidney transplant, but I don't shout it out. I don't need contact with other patients with a kidney transplant, I am like anybody else. I am independent and try to do my best with taking my medication, sometimes it is hard to comply. It is important for healthcare professionals to remind you of the importance of your medication, so you try harder. I can do anything and do not feel limitations. I trust that the doctor knows what is best.

Not at All | not | A little | good | Very good

☐ ☐ ☐ ☐ ☐

D

I think it is more important to live my life than to be compliant. I am not so accurate with my medication, I sometimes forget. I think you can forget your pills sometimes, nothing bad will happen. I find it difficult to say no to my friends, I want to do the same things like they do. My life is all about my disease enough. I have side-effects of the medication. My doctor or nurse may confront me with my noncompliance, so I start realizing what I am doing. My parents are interfering to much with my life. I don't worry about the future, my life is now.

Not at All | not | A little | good | Very good

☐ ☐ ☐ ☐ ☐

Dankwoord

Dankwoord

Eindelijk is het dan zover, ook ik mag een dankwoord schrijven. Het voltooien van een proefschrift is een hele 'bevalling'. Het dankwoord biedt mij een gelegenheid om stil te staan en dankbaar te zijn voor de mensen die mij geholpen hebben in mijn carrière, of een inspiratie bron of rolmodel zijn geweest, vaak zonder dat diegene zich daar bewust van is geweest.

Allereerst ben ik dank verschuldigd aan alle niertransplantatiepatiënten die hebben deelgenomen aan de studies, letterlijk van jong tot oud. Jullie hebben me een kijkje gegeven in jullie leven en dank voor de eerlijke openhartige gesprekken over het moeilijke onderwerp therapietrouw.

Zonder mensen te kort willen doen wil ik toch een aantal mensen in het bijzonder noemen die ik dankbaar ben.

Mijn 'serieuze' carrière begon op de middelbare school waar mijn toenmalige leraar Engels meneer De Vries zei dat ik vast achter de kassa van de HEMA zou eindigen. Nu heb ik niks tegen het beroep caissière, maar ik heb altijd in mijn achterhoofd het idee gehad dat mijn tijd nog zou komen, dankzij meneer de Vries ben ik toch niet die richting opgegaan. Al heb ik wel enige jaren met veel plezier bij de HEMA gewerkt om wat bij te verdienen.

Na de middelbare school volgde de HBO-V opleiding (duaal leren/werken) in Rotterdam en ben ik gaan werken als verpleegkundige op transplantatieafdeling 10 midden. Wat een fantastische tijd heb ik daar mogen beleven met veel bijzondere mensen, enkelen die ik daar ontmoet heb blijken vriendinnen voor het leven te zijn (Annemiek, Femke & Debbie).

Na een open sollicitatie werd ik door professor Weimar aangenomen en ben ik de opleiding tot Master of Advanced Nursing Practice (MANP) gaan volgen in 2004. In 2006 afgestudeerd als nurse practitioner, waarna ik mij in 2012 volgens de wet verpleegkundig specialist mocht noemen.

Mijn promotor, Prof.dr. W. Weimar, beste Willem, allereerst bedankt dat ik het vertrouwen kreeg om als eerste nurse practitioner (nu verpleegkundig specialist) te mogen beginnen op de afdeling niertransplantatie. Bedankt voor alle kansen die u mij gegeven hebt. Ik weet nog goed dat u tegen me zei we gaan iets onderzoeken en dan ga je daar een abstract over schrijven. Ik wist niet eens wat een abstract was. Vele abstracts en mooie congresreizen later is hier dan het resultaat. Soms had ik wat overredingskracht nodig, er waren immers

nog zoveel andere leuke dingen, maar nu dan toch de eerste verpleegkundig specialist van het Erasmus MC die mag promoveren. Bedankt voor de mooie tijd, ik ben er trots op dat u mijn promotor bent, ik had geen andere willen hebben!

Mijn copromotor, dr. Emma Massey, wat fijn om jou als collega te hebben en dat je mijn copromotor wilde zijn. Ik heb enorm veel van je geleerd, ik ken je als een ambitieuze vrouw waar ik een voorbeeld in zie. Je weet jezelf en daarmee het hele team op de kaart te zetten. Verder wil ik je bedanken voor onze fijne samenwerking, waarbij ik meer over de praktische vraagstukken nadenk en jij over de theorie. Je maakt altijd tijd voor me vrij. Ook bedankt voor het corrigeren van mijn Engels, dat moet soms best grappig zijn geweest.

Willij Zuidema, ik had het in het begin best lastig in mijn nieuwe functie als pionier en kon altijd bij je terecht. Bedankt daarvoor, ook heb ik dankzij jou veel mensen leren kennen en stimuleerde je mijn betrokkenheid bij bepaalde werkgroepen buiten de eigen niertransplantatieafdeling en stond je er voor open dat ik voorzitter van de LWTV (landelijke werkgroep transplantatie verpleegkundigen) werd.

Ook Adela den Breejen was een steun voor me tijdens mijn opleiding tot verpleegkundig specialist, bedankt dat je mijn verpleegkundig leermeester wilde zijn.

Tijdens de opleiding tot verpleegkundig specialist kwam ik in contact met Susan Jedeloo en AnneLoes van Staa van de Hogeschool Rotterdam. Zij waren diegenen die me begeleiden tijdens de masterthese en met hen heb ik mijn eerste artikel gepubliceerd, waarvoor dank. Met AnneLoes ben ik altijd contact blijven houden, en ik hoop dat we nog vele jaren blijven samenwerken. Ik vind het een eer om jou in de commissie te hebben.
Via Susan leerde ik Job van Exel kennen, de Nederlandse expert op het gebied van Q-methodologie (samen met Gjalt). Job bedankt voor al je advies en geduldige uitleg en de gezellige Q-congressen. Ik kan altijd een beroep op je doen! Ik heb veel van je geleerd.

Prof.dr. Teun van Gelder, jij was de eerste nefroloog die het wel aandurfde om zijn transplantatiepatiënten te delen met de verpleegkundig specialist, waarvoor dank. Ook al heb je het druk, ik krijg altijd een reactie van je via telefoon, mail of de app. Ook dat je mijn stukken naleest en van feedback voorziet. Wat fijn dat je in de commissie zit.

Prof.dr. Jan van Busschbach, Prof.dr. Sabina de Geest, Prof.dr. Jan van Saase en Prof.dr. Jan IJzermans bedankt dat jullie in de commissie willen deelnemen en tijd hebben gemaakt om mijn proefschrift door te nemen.

Alle verpleegkundig specialisten in het Erasmus MC bedankt voor jullie inzet om de functie verpleegkundig specialist neer te zetten binnen het ziekenhuis, vorderingen lijken soms zo langzaam te gaan, maar als we terugblikken hebben we met z'n allen al zo veel voor elkaar gekregen. Ik ben er trots op om als eerste verpleegkundig specialist te mogen promoveren binnen het Erasmus MC, ik hoop dat nog velen van jullie mij volgen!

Bedankt alle collega's binnen het LWTV netwerk voor de fijne contacten, gezellige workshops, adviezen, bedankt voor het vertrouwen en dat ik jullie voorzitter mocht zijn.

Verder wil ik al mijn (oud) collega's bedanken voor de gezelligheid, de fijne gesprekken, en de "printer" praatjes.
De dames van de poli; Heidi, Linda, Marja, Saskia en Silvana.
De coördinatoren; Annette, Ingrid, Jacqueline, Karin, Saliha en Sandra, bedankt voor onze prettige samenwerking. Ook maatschappelijk werker Nico Tronchet bedankt voor de samenwerking.
De research(verpleegkundigen): Nelly, Monique, Marieken en Brigitte, bedankt voor de gezelligheid en interesse in mijn onderzoek. Ook voor de Nederlandse les waar ik regelmatig om vraag.
De database club; Judith, Mirjam en Tessa. Judith, ik kan altijd bij je aankloppen indien ik weer een nieuw lijstje met eisen uit de database wil, en jij tovert dit dan zo weer in elkaar. Bedankt daarvoor (en blijf daar vooral mee doorgaan). Mirjam wil ik in het bijzonder bedanken voor het mede afnemen van de Q-methodologie, nuttige tips over Endnote tot alle vragen over de Kaplanmeier.
Verder dank aan Marry (voor de ervaringsverhalen), Saida, Mathilde, Frederike, Lotte (een mooi voorbeeld hoe te promoveren), Dorthe en Marian voor de gezelligheid.
De D-gang mannen: Paul en Jan, bedankt voor jullie humor. Jan, jij ziet alles, of ik het nu leuk vind of niet, en Paul bedankt voor het vertrouwen dat jij wel gewoon bij me in het vliegtuig stapt, dat durft niet iedereen.
Alle nefrologen bedank ik voor de prettige samenwerking, met in het bijzonder de pre-transplantatie nefrologen Jacqueline, Joke en Marcia. Ook Martijn dank ik voor zijn onderwijsmomenten en ondersteuning bij mijn post transplantatiepoli. Michiel Betjes bedankt voor de vrijheid om te promoveren. Ook alle medewerkers van het transplantatielab bedankt voor het afnemen van de spiegelbepalingen die ik gebruikt heb in mijn onderzoek. Alle medewerkers van de afdeling heelkunde voor de prettige samenwerking.

Dit proefschrift zou er nooit gekomen zijn zonder de hulp van psychologiestudenten Denise Beck en Roshni Khemai, dankzij de EBCN (Evidence Based Care for Nurses) beurs konden zij de data verzamelen en kon ik rustig met zwangerschapsverlof. Dankzij de kundigheid en

accuraatheid van deze dames kon ik dat met een gerust hart overlaten. Denise wat leuk dat je na je afstuderen een collega van mij geworden bent en de verpleegkundig specialist nu een belangrijke rol in jouw onderzoeksproject speelt.

Dan wil ik in het bijzonder mijn paranimfen bedanken, mijn 2 collega's Louise en Marleen. Heb altijd gezegd dat mocht ik ooit gaan promoveren dat zij mijn paranimfen mochten zijn. Nu is het dan eindelijk zover. Ook jullie hebben een bijdrage geleverd aan dit proefschrift met het afnemen van de Q. Mijn werk begon pas echt leuk te worden toen ik jullie als collega's kreeg. Ik ben nu eenmaal een teamplayer en heb mensen in mijn omgeving nodig die me stimuleren. Mede dankzij jullie kunnen we de functie en continuïteit van ons beroep pas goed vorm geven. Ik ben er trots op als je ziet wat we in die jaren allemaal al bereikt hebben. We zijn alle drie verschillend maar dat maakt onze samenwerking des te sterker, we vullen elkaar aan en zijn een hecht team. Ook buiten het werk kunnen we het goed met elkaar vinden. Ik hoop met jullie nog lang samen te mogen werken. Bedankt dat jullie achter me willen staan op deze belangrijke dag.

In mijn persoonlijk leven dank ik al mijn vrienden en familie voor een luisterend oor en de interesse die jullie in mijn onderzoek hebben getoond. Thijs, bedankt voor het maken van de mooie kaft. Mijn hechte vriendenkring bedank ik voor de gezelligheid en gekkigheid die we uithalen, mijn BFF Hedwig, Femke & Kevin, Debbie & Hans, Annemiek & Michiel. Jullie geven me energie!
Mijn broer Remco en schoonzus Marit, bedankt voor jullie interesse. Mijn andere schoonzus Chantalle en zwager Paul. We hebben samen al heel wat doorstaan. Mijn lieve oma, die trots is op alles wat ik bereikt heb.
Overige vrienden, familie, kennissen, bedankt voor jullie interesse.

Mijn ouders dank ik voor de fijne warme jeugd die ze me gegeven hebben. Ze hebben me geleerd om een zelfstandige sterke vrouw te zijn met een eigen mening. Ik weet dat jullie trots op me zijn, wie had gedacht dat ik ooit zou promoveren. Mijn doorzettingsvermogen heb ik van jullie. Jullie hebben me altijd gestimuleerd om de kansen te grijpen die er liggen. Ik weet dat ik altijd op jullie kan terugvallen, tegelijkertijd hebben jullie mij geleerd dat ik het wel red. Wat fijn dat we in het mooie Brabant zijn gaan wonen en we iets dichter bij elkaar wonen. Wat heerlijk mam om te zien hoe je elke week op onze kinderen past en hen leert wat je mij hebt geleerd, ik hoop nog heel lang van jullie beiden te genieten.

Xavier bedankt, met jou deel ik mijn leven, reislust, hobby's, verdriet, geluk, huishouden, blijdschap, humor (gedeeltelijk dan) en nog veel meer. Wij kunnen alles aan zolang we het samen blijven doen. Je hebt me altijd gestimuleerd om dit boekje te schrijven en vertelt het

trots tegen iedereen die het maar wil horen, want je vindt het maar wat stoer om straks een doctor als vrouw te hebben.
We hebben samen al heel wat meegemaakt, en ik weet dat je mijn rugzak altijd de Machu Picchu op zal dragen. The sky is the limit, maar niet voor ons….

Samen hebben we drie prachtige kinderen gekregen, waar we intens van genieten. Ze zijn alle drie unieke temperamentvolle kinderen, dat moet ook wel met ons als ouders.
Lieve Evi, Dex & Cas, mama houdt van jullie!

10