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ORIGINAL ARTICLE

Severe fatigue after kidney transplantation: a highly prevalent, disabling and multifactorial symptom

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Summary

Fatigue is a common symptom of patients with chronic kidney disease, but seldom investigated after transplantation. We determined the prevalence, impact and related factors of severe fatigue in kidney transplant recipients (KTRs). Medical records and questionnaires were used to assess kidney function, donor characteristics, fatigue (Checklist Individual Strength), functional impairments (Sickness Impact Profile), work status, body mass index (BMI), pain, depressive symptoms, social support and sleeping problems in 180 participating KTRs. KTRs were compared with sex- and age-matched population-based controls. KTRs were significantly more often severely fatigued (39%) compared to matched controls (22%; $P = 0.001$). Severely fatigued KTRs had significantly more functional impairments than nonseverely fatigued recipients (effect size ≥ 0.7) $P < 0.001$, and less often a paid job (27% vs. 48%, $P = 0.005$). Univariate analysis showed that severely fatigued KTRs received more often a kidney from a deceased donor, had a higher BMI, more pain, discrepancy in social support, depressive symptoms and sleeping problems. In a multivariate analysis ($n = 151$) the latter two associations remained significant. Severe fatigue is a highly prevalent and disabling symptom in KTRs. Moreover, severe fatigue after kidney transplantation is more strongly related to behavioural and psychosocial factors than specific transplantation-related factors. Findings have implications for fatigue management.

Introduction

Fatigue is a common symptom in patients with chronic kidney disease [1,2]. The prevalence of fatigue is 60% or higher in patients on maintenance dialysis [1–3]. The importance of fatigue is emphasized by the finding that 94% of the patients were willing to undergo more frequent dialysis for an increase in energy level, while only 19% would undergo more frequent dialysis for an increase in survival [4]. When patients receive a kidney transplantation, their renal function is restored and it is expected that most patients will recover from fatigue. This is supported by cross-sectional studies which found that patients are less fatigued after kidney transplantation compared to patients before transplantation [5,6]. Even though fatigue seems to decrease after kidney transplantation, sparse studies indicate that kidney transplant recipients (KTRs) experience more fatigue than healthy controls [7,8]. Rodrigue *et al.* [6] even classified 59% of recipients with high fatigue severity, based on an earlier defined cut-off score for clinically relevant fatigue determined in a sample of healthy women [9].

So compared to healthy individuals KTRs seem to experience more fatigue. However, it can be debated whether this comparison gives a realistic view on the problem of fatigue in KTRs. Because a substantial proportion of the general population suffer from a chronic illness, the comparison with healthy individuals might give a more problematic view on fatigue in kidney transplantation recipients than is justified. Therefore, it seems worth investigating

how many patients suffer from severe fatigue after kidney transplantation compared to the general population.

In KTRs as well as in patients before transplantation, it has been demonstrated that fatigue is associated with lower quality of life [6]. However, it is unknown how large the impact is of severe fatigue on functional impairment and work status.

It is generally assumed that fatigue in KTRs is usually caused by specific transplantation-related factors, such as insufficient kidney function, and type of immunosuppression [10]. However, scarce research specifically aimed at fatigue does not confirm this. High body mass index (BMI), mood disturbance and poor sleep quality were associated with high fatigue severity, while type of immunosuppression (sirolimus versus tacrolimus), primary diagnosis, disease duration and the time since transplantation were not related with fatigue [6]. Unfortunately, indicators for renal function were not included in this study, and therefore it is unclear whether these indicators, such as proteinuria, serum creatinine level, former rejections or biopsies are related to fatigue after kidney transplantation.

Fatigue in KTRs is most likely related to various factors. In addition to specific transplantation-related factors, also behavioural and psychosocial factors probably play a role. Fatigue studies in other patient groups have shown that fatigue is multifactorial, in which nonspecific disease-related factors, such as pain [11–16], depression [3,13,14,17], sleeping problems [3,11,15,16] and low social support [12,13,16,18–21] are relevant.

This study had three aims. Our first aim was to determine the prevalence of severe fatigue after kidney transplantation compared to sex- and age-matched population-based controls. Our second aim was to determine the impact of severe fatigue by comparing severely fatigued KTRs with nonseverely fatigued recipients on functional impairments and work status. We hypothesized that severely fatigued recipients would be significantly more functionally impaired and had less often a paid job compared to nonseverely fatigued recipients and that this difference would be large. Third, we investigated the relationship between fatigue and specific transplantation-related factors and nonspecific somatic, behavioural and psychosocial factors in KTRs. More specifically, we determined whether kidney function (proteinuria, serum creatinine level, former rejections, undergone biopsies), characteristics of the donor (living versus deceased, donor age), BMI, pain, depressive symptoms, discrepancy in social support and sleeping problems were related to severe fatigue.

Methods

Patients

Patients who received a kidney transplantation in the last 3 years at the Radboud University Nijmegen Medical Centre were approached. Recipients had to be 18 years or older, able to speak, read, write and understand Dutch and not currently treated with dialysis for renal failure. The control group were drawn from a cohort group of panel members of CentERdata [22]. CentERdata is a Dutch research institute at Tilburg University, specialized in online survey research. The CentERpanel is an online panel consisting of more than 2000 Dutch household's representative of the adult Dutch population with respect to age, sex, education and social economic status.

Procedure

All eligible KTRs received an information letter in November 2011. They were requested to indicate whether they wanted to participate by filling in an informed consent form and returning it using a prepaid envelope. Recipients who returned the informed consent form received the questionnaires by mail or e-mail depending on their preference. Recipients who agreed to participate, but did not return the questionnaires were send one reminder by mail, and two by e-mail. In the summer of 2012 the panel of CentERdata were requested to complete the Checklist Individual Strength (CIS). As this observational study used questionnaires not forming an invasion of the participant's integrity, and medical data earlier collected for other purposes, it did not fall under the remit of the Medical Research Involving Human Subjects Act.

Instruments

Demographical characteristics, work status and BMI were collected using a questionnaire. Proteinuria, serum creatinine level, number of rejections, prior dialysis, duration of dialysis, time since transplantation, living versus deceased donor, and donor age, types of immunosuppression and haemoglobin were all collected from medical records around the time when patients completed the questionnaires.

Severe fatigue was assessed using the subscale fatigue of the CIS [23,24]. This subscale consists of eight items. Each item is scored on a 7-point Likert scale. Scores range from 8 to 56. The CIS was used in this study because with this instrument it is possible to distinguish severe fatigue from nonsevere fatigue. Severe fatigue is defined as a score of 35 or higher on the CIS fatigue, which is two standard deviations above the mean score of that of the original healthy reference group [25]. The Dutch version of the CIS is well validated [24,25], sensitive to detect change and often used in research in patients with various illnesses or conditions, such as cancer [18], neuromuscular diseases [26], stroke [27], rheumatoid arthritis [28] and chronic fatigue syndrome [29].

Functional impairments were assessed using the Sickness Impact Profile 8 (SIP). The SIP consists of eight subscales; sleep and rest, homemaking, mobility, social interactions, ambulation, leisure activities, alertness behaviour and work limitations with higher scores indicating more impairments. The SIP has a high reliability, good construct, convergent and discriminant validity and is validated in the Dutch population [30,31]. The impact of fatigue on functional impairments was determined by evaluating the effect sizes of the differences in functional impairments between severely and nonseverely fatigued KTRs (see Statistical analyses section).

Pain severity and impact was assessed using the pain subscale of the Health Survey Short Form-36 (SF-36). Scores range from 0 to 100 with lower scores indicating more pain. The Dutch language version of the SF-36 has been proved to be a reliable and valid instrument in the general population and in patients with a chronic disease [32].

Depressive symptoms were assessed by the Beck Depression Inventory–Primary Care (BDI-PC) [33]. This is a seven item questionnaire with scores ranging from 0 to 21. A score of four or higher on the BDI-PC is indicative for a clinical depression [34]. The BDI-PC is based on a set of nonsomatic items from the BDI-II [35].

Discrepancy in social support was assessed using the Van Sonderen Social Support Inventory-subscale Discrepancy [36]. The items measure the amount of (dis)satisfaction with the social support the respondent indicated to receive. Scores range from 8 to 32 and higher scores indicate a larger discrepancy. Sleeping problems were assessed using the subscale sleep/rest of the SIP [30,31]. The participants were asked to complete all six questionnaires with in total 157 items.

Statistical analyses

Descriptive statistics were used for describing demographical and treatment-related characteristics of the sample and the prevalence of severe fatigue. KTRs were matched by age and sex with the same number of population-based controls from the sample (n = 2300) of CentERdata. Precision matching was performed with STATA/SE 12.1.

To compare KTRs with matched population-based controls, and severely with nonseverely fatigued recipients on functional impairments and work status, paired t-tests and chi-square were used. The impact of severe fatigue on functional impairments was assessed by calculating effect sizes. Effect sizes, Cohen's d, were calculated by mean1 − mean2/SD_{pooled}, where $SD_{pooled} = \sqrt{[(SD1^2 + SD2^2)/2]}$, where by means and standard deviations of functional impairments from severely and nonseverely fatigued recipients were used. Effect sizes of 0.2 are considered small, 0.5 as moderate and 0.8 or higher as large [37,38].

The estimated glomerular filtration rate (eGFR) (ml/min) was calculated with the Cockcroft–Gault formula [140 − Age (years)] × Weight (kg) × (0.85 if female)/0.81 × Serum creatinine (μmol/l) [39]. To test whether there were significant differences between severely and nonseverely fatigue recipients on proteinuria, serum creatinine level, former rejections, undergone biopsies, living versus deceased donor, donor age, BMI, pain, depressive symptoms, discrepancy in social support, and sleeping problems, univariate (t-tests and chi-square) and multivariate (logistic regression analysis) analyses were performed.

Results

In total, 278 eligible KTRs were approached. Of the 200 recipients that agreed to participate, 180 returned the questionnaires (see Fig. 1). The response rate was 65%. Participants who returned the questionnaires (n = 180) were on average 6 years older (SD 13) than nonresponders (n = 98) $P < 0.001$, but there were no differences on sex ($P = 0.634$) or time since transplantation ($P = 0.446$). No other data were collected from nonresponders. From the 180 participants, 155 complete data were obtained, while 25 participants missed a subscale or questionnaire. Descriptions of demographical and treatment-related factors are given in Table 1. The time between sending the invitation letter and

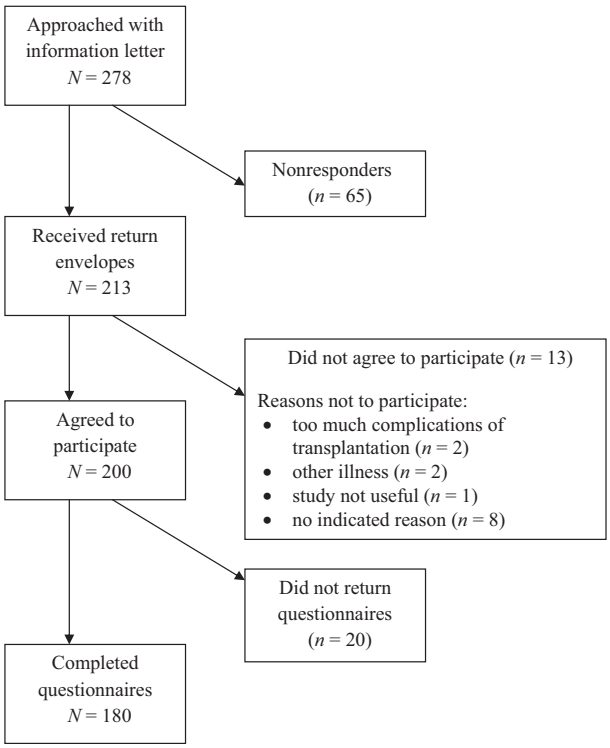

Figure 1 Flow chart of approached patients.

Table 1. Description of demographical and treatment-related factors of kidney transplant recipients.

	Mean ± SD	Number of participants (%)
Age (years)	54 ± 12	
Education (1 = low, 7 = high)	4.0 ± 1.7	
Sex		
Male		119 (66%)
Female		61 (34%)
Marital status		
Married		135 (75%)
Not married		42 (24%)
Unknown		2 (1%)
Prior dialysis		
Yes		131 (73%)
Duration of dialysis (days)	1256 ± 1189	
No		49 (27%)
Time since transplantation (years)	1.6 ± 0.9	
Type of immunosuppression		
CNI		152 (84%)
tac/pred		76
tac/pred/mmf		42
tac/other		8
csa/pred and/or aza		20
csa/pred/mmf		6
Other		28 (16%)
siro/pred		9
siro/pred/aza or mmf		3
mmf/pred		10
Other		6
Haemoglobin level (g/dl)	12.9 ± 2.0	
Unknown		1 (1%)
Diabetes mellitus		
Yes		21 (12%)
No		159 (88%)

SD, standard deviation; CNI, calcineurin inhibitors; mmf, mycophenolate mofetil; aza, azathioprine; csa, cyclosporine; pred, prednisone; siro, sirolimus; tac, tacrolimus.

the date patients were seen by their physician was on average 3.5 months (SD 4.1). There were no significant differences between severely and nonseverely fatigued recipients on demographical and treatment-related variables (data not shown). The difference on severe fatigue between users of noncalcineurin inhibitors (46%), users of cyclosporine in combination with other immunosuppressants (34%) or users of tacrolimus in combination with other immunosuppressants (58%) was borderline significant ($P = 0.05$).

Prevalence and impact of severe fatigue

Of all KTRs, 39% [95% confidence interval (CI) 32–46] were severely fatigued. This percentage was significantly higher than in the matched control group (22%, 95% CI 16–28, $P = 0.001$). Severely fatigued recipients were significantly more impaired compared to nonseverely fatigued recipients on all eight domains of functioning assessed. The sizes of the differences on five subscales were large in effect, while on three subscales it was moderate. The effect size on the SIP total was large (see Table 2). Furthermore, severely fatigued recipients had significantly less often (27%) a paid job compared to nonseverely fatigued recipients (48%) $P = 0.005$.

Fatigue-related factors

Univariate analyses showed that severely fatigued renal transplant recipients received significantly more often a kidney from a deceased donor, were more often overweight or obese, reported more pain and sleeping problems, had more depressive symptoms and experienced a higher discrepancy in social support than nonseverely fatigued recipients (see Table 3). Of the 39% severely fatigued recipients 12% had clinically relevant depressive symptoms. In total, 13% had clinically relevant depressive symptoms. The difference between severely and nonseverely fatigued recipients was borderline significant on serum creatinine level. The logistic regression analysis ($n = 151$) showed that having clinically relevant depressive symptoms and more sleeping problems (odds ratio 9.70 and 1.02 respectively; $P = 0.013$ and ≤ 0.001) were most strongly related to severe fatigue, but donor type, BMI, pain or social support were no longer significantly related to severe fatigue.

Discussion

Sparse studies already indicated that KTRs experienced more fatigue compared to healthy individuals, but a comparison with the general population was never made. Results of this study showed that severe fatigue is a highly prevalent symptom in KTRs and associated with more functional impairments even in comparison with the general population. Moreover, severe fatigue was most strongly related to behavioural and psychosocial factors rather than specific transplantation-related factors.

Our first aim was to compare KTRs with the general population on the prevalence of severe fatigue. We found that as many as 39% of the recipients were severely fatigued compared with 22% of the sex- and age-matched population-based control group. Our results revealed a lower percentage of severe fatigue than previously found in comparison to healthy individuals [6]. The discrepancy could be explained by the fact that a different questionnaire was used, and that the chosen cut-off score was determined with a different method.

Our study also indicated that severe fatigue is a disabling symptom for KTRs. This conclusion is based on the findings that severely fatigued recipients experienced significantly and largely more functional impairments than

Table 2. Difference between severely fatigued and nonseverely fatigued kidney transplant recipients on functional impairments in daily life.

	Nonseverely fatigued patients after kidney transplantation, mean (SD)	Severely fatigued patients after kidney transplantation, mean (SD)	Size of the difference Effect size Cohen's *d*
SIP sleep and rest (*n* = 179)	27 (39)	108 (90)*	1.2[L]
SIP homemaking (*n* = 179)	31 (46)	114 (108)*	1.0[L]
SIP mobility (*n* = 179)	6 (23)	63 (105)*	0.7[M]
SIP social interactions (*n* = 179)	42 (90)	192 (216)*	0.9[L]
SIP ambulation (*n* = 179)	17 (41)	84 (111)*	0.8[M]
SIP leisure activities (*n* = 179)	23 (40)	94 (81)*	1.1[L]
SIP alertness behaviour (*n* = 179)	34 (73)	117 (155)*	0.7[M]
SIP work limitations (*n* = 174)	62 (125)	164 (170)*	0.7[M]
SIP total (*n* = 174)	242 (274)	950 (707)*	1.3[L]

SIP, Sickness Impact Profile; SD, standard deviation, L; large effect; M, moderate effect.
Higher scores indicate more functionally impaired, **P* < 0.001.

Table 3. Difference between severely fatigued and nonseverely fatigued kidney transplant recipients on somatic and psychological factors.

	Nonseverely fatigued patients after kidney transplantation (*n* = 109)	Severely fatigued patients after kidney transplantation (*n* = 70)	Overall	*P*-value
Creatinine level (μmol/l) (*n* = 179)	130 (37)	143 (50)	135 (43)	0.05
Glomerular filtration rate* (ml/min) (*n* = 177)	63 (19)	65 (29)	64 (29)	0.70
Proteinuria level (g/l) (*n* = 168)	0.11 (0.25)	0.16 (0.23)	0.13 (0.24)	0.23
Number of rejections (*n* = 179)				
0	74 (63%)	44 (37%)	118 (65%)	0.49
>0	35 (57%)	26 (43%)	61 (34%)	
Number of biopsies (*n* = 179)				
0	70 (64%)	40 (36%)	110 (61%)	0.34
>0	39 (57%)	30 (43%)	69 (39%)	
Donor type (*n* = 179)				
Living	74 (69%)	33 (31%)	107 (60%)	**0.01**
Deceased	35 (49%)	37 (51%)	72 (40%)	
Donor age (*n* = 176)	53 (12)	51 (12)	53 (12)	0.23
BMI (*n* = 176)				
<25	60 (71%)	24 (29%)	84 (48%)	**0.03**
≥25 to >30	37 (54%)	31 (46%)	68 (39%)	
≥30	11 (46%)	13 (54%)	24 (13%)	
Sf 36 pain (*n* = 177)	93 (15)	68 (27)	84 (23)	**<0.001**
BDI-pc (*n* = 173)				
≥4	2 (1%)	21 (12%)	23 (13%)	**<0.001**
SSL-d (*n* = 172)	9.8 (2.8)	11.4 (3.8)	10 (3.3)	**0.003**
SIP sleep and rest (*n* = 179)	27 (39)	108 (90)	58 (75)	**<0.001**

SD, standard deviation; BMI, body mass index; SF-36, Health Survey Short Form-36; BDI-PC, Beck Depression Index–Primary Care; SSL-d, Social Support List–Discrepancy; SIP, Sickness Impact Profile.
Values are expressed mean (SD) or *n* (%).
Bold *P*-values are significant (*P* < 0.05).
*Estimated glomerular filtration rate was calculated with the Cockroft–Gault formula.

nonseverely fatigued recipients. Moreover, severely fatigued recipients also had a lower chance of having a paid job. The notion that severe fatigue is a symptom associated with substantial impairments is in accordance with other quality of life studies [6,7,10,40].

Finally, we found that behavioural and psychosocial factors were more strongly related to severe fatigue in KTRs than specific transplantation-related factors. In this study, we specifically investigated the relationship between kidney function and fatigue, but an association between proteinuria,

serum creatinine level, former rejections, undergone biopsies and severe fatigue could not be confirmed. The identified factors related to severe fatigue were having received a kidney from a deceased donor, being overweight, more pain, depressive symptoms, sleeping problems and a discrepancy in social support. Depressive symptoms and sleeping problems were most strongly related to severe fatigue, while the other assessed factors were no longer significant in multivariate analysis.

Our finding that severe fatigue was related to depressive symptoms, sleeping problems and also overweight is in accordance with the study of Rodrigue *et al.* [6]. The prevalence of obesity in our sample (13%) seems to lie in the same range as the Dutch population (11% in 2011) [41]. On the one hand, one might expect a lower prevalence of obesity in KTRs, because patients with chronic kidney disease having a BMI larger than 40 are generally ineligible for kidney transplantation. On the other hand, it is also not uncommon for patients to gain weight after kidney transplantation. Depressive symptoms were strongly related to severe fatigue, but it could not completely explain the presence of severe fatigue. Of the 39% severely fatigued recipients more than two third did not have clinically relevant depressive symptoms.

This is the first study that identified pain, social support and having received a kidney from a deceased donor as fatigue-related factors. These relationships with fatigue were not confirmed in multivariate analysis. This could be explained by the fact that this analysis could only be performed in a subgroup because of missing data. However, various quality of life studies indicated that these factors are relevant for renal transplant recipients. In one quality of life study a relationship between pain and vitality was found [42]. Unfortunately, we did not assess the location of the pain and therefore we do not know whether the pain is related to the transplantation or other causes. However, pain scores in our sample do not seem to be higher than in the general population.

The relationship between perceived discrepancy in social support and fatigue is supported by another quality of life study. Perez-San-Gregorio *et al.* showed that transplant patients whose relatives presented symptoms of anxiety and depression after transplantation had a worse quality of life, including more fatigue [43]. They argue that it could be that patients do not receive the support they need from their relatives, causing negative repercussions on patients' quality of life.

How having received a kidney from a deceased donor contributed to severe fatigue in KTRs can only be debated, because this is the first study that found this relationship. There are physiological and psychosocial explanations possible. It might be that recipients who received a kidney from a living donor experience less often fatigue because this type of transplantation has better outcomes in terms of complications and hospitalization compared to recipients who received a kidney from a deceased donor. Psychosocial factors might also play a role. Perhaps recipients who received a kidney from a living donor might be more sociable, because they are capable to interest others for their problems. This sociability might also be protective of severe fatigue after transplantation. Factors that are also worth investigating as fatigue maintaining factors could be avoidance coping strategies [44], worrying about transplant, or viability of graft [45] as these psychosocial factors contributed to worse quality of life outcomes in KTRs.

Limitations of this study must be acknowledged. This study has a cross-sectional design, and therefore only gives insight into associations with severe fatigue. Although the causality of the relationships could not be determined, previous studies have shown that severe fatigue is related to functional impairments, and that when fatigue is reduced by therapy functional impairments also decrease [46,47].

We need to be aware that the group of respondents might be a biased group, because the response rate was moderate. About a third of the invited individuals did not respond to the invitation letter nor did return the questionnaires. Furthermore, it might be that the data missing were not at random. For example, ten participants did not complete the BDI and three participants did not fill in their weight. Possibly, the questions itself influenced participants choice not to answer the questions. Unfortunately, we are unable to determine if this caused a selection bias, firstly because we don't know the somatic, treatment and fatigue-related characteristics of the recipients who did not respond to the invitation, and secondly the group of recipients who were not willing to participate is too small to find significant differences with recipients who did participate. It is possible that recipients who experience fatigue responded more often, because they want their symptom to be acknowledged, but it is also possible that fatigued recipients responded less often, because of limited motivation to participate. Furthermore, one should be cautious when generalizing these findings to non-Dutch populations.

Another limitation is the reliance on self-reported data. However, fatigue, our outcome measure, but also depressive symptoms, and pain can only be assessed by self report. Using a reliable and well-validated questionnaire was the best available method to assess these concepts.

In the current study, the difference between severely and nonseverely fatigued KTRs on creatinine level was borderline significant, but it is not expected that the relationship between fatigue and kidney function will become a strong one. Especially because we did not find a significant difference between severely and nonseverely fatigued KTRs on the mean values of the eGFR and also because we did not find that values lower than 60 ml/min occurred more often in severely fatigued KTRs than in nonseverely fatigued KTRs.

For clinical practice, it is helpful to distinguish nonsevere fatigue from severe fatigue. However, using a cut-off might raise the question whether analyses in which fatigue was evaluated as a continuum would have retrieved the same results. Re-analyses did show a different outcome on creatinine level. When fatigue was assessed as a dichotomous variable the relationship with creatinine was borderline significant, when assessed as a continuous variable it was significant. However, the correlation between creatinine and fatigue was not very strong. Moreover, the relationship between fatigue and all other assessed factors remained unchanged irrespectively on whether fatigue was assessed as a continuum or dichotomized.

In summary, this study demonstrates that a substantial subgroup of KTRs suffer from disabling severe fatigue. Moreover, it indicates that the fatigue is more strongly related to behavioural and psychosocial factors than to specific transplantation-related factors. New in this study is the fact that the relationship between indicators for kidney function and fatigue was investigated, but not confirmed. Our findings could have clinical implication for future treatment of fatigue in KTRs. When a patient continues to experience severe fatigue after kidney transplantation, it is probably not frequently caused by insufficient kidney function. Based on fatigue studies in other patient groups, it might be that the model of precipitating and perpetuating factors for fatigue is also applicable for KTRs. According to this model kidney insufficiency, the transplantation, and possibly complications are fatigue precipitating factors, while other factors, mostly cognitive behavioural factors, maintain the fatigue after kidney transplantation [48,49]. These fatigue maintaining factors can be addressed in cognitive behaviour therapy for severe fatigue [46,47,50]. Two of these fatigue maintaining factors, sleeping problems and discrepancy in social support are identified in the current study. For future research, it would be worth to investigate which other factors, such as low self-efficacy (sense of control over fatigue), somatic attributions (attributing the cause of fatigue to a somatic cause) and catastrophizing regarding fatigue (considering fatigue as a catastrophe, the expectation of an unbearable outcome when one feels fatigued) and inactivity, maintain the fatigue in KTRs. If this can be confirmed, a therapy can be developed to reduce the fatigue in patients after kidney transplantation.

Authorship

MMG: performed the study, analyzed and interpreted data, and wrote the manuscript. AJH: designed the study, collected data, interpreted data, contributed to the discussion, reviewed and edited the manuscript. GB: designed the study, interpreted data, contributed to the discussion, reviewed and edited the manuscript. LB: collected data and reviewed the manuscript. HK: interpreted data, contributed to the discussion, reviewed and edited the manuscript.

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