Predictors and consequences of fatigue in prevalent kidney transplant recipients

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Title

The Predictors and Consequences of Fatigue in Prevalent Kidney Transplant Recipients

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Author's Contributions

Winnie Chan, Jos A Bosch, David Jones, Nicholas Inston, Andrew McClean, Lorraine Harper and Richard Borrows participated in research design. Winnie Chan, Jos A Bosch, David Jones, Philip G McTernan, Lorraine Harper, Anna C Phillips and Richard Borrows participated in the writing of the paper. Winnie Chan, Okdeep Kaur, Sue Moore and Richard Borrows participated in the performance of the research. Winnie Chan and Richard Borrows participated in data analysis.

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Conflict of Interest

The authors declare no conflicts of interest.

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Abbreviations

Kidney Transplant Recipients **(KTRs)**

Quality of Life **(QoL)**

Multi-Dimensional Fatigue Inventory **(MFI-20)**

General Fatigue **(GF)**

Physical Fatigue **(PF)**

Reduced Activity **(RA)**

Reduced Motivation **(RM)**

Mental Fatigue **(MF)**

Medical Outcomes Study Short Form **(SF-36)**

Kidney Transplantation **(KT)**

Index of Co-Existent Disease **(ICED)**

Chronic Fatigue Syndrome **(CFS)**

Fat Tissue Index **(FTI)**

Lean Tissue Index **(LTI)**

Hospital Anxiety and Depression Scale **(HADS)**

Pittsburgh Sleep Quality Index **(PSQI)**

Multiple Sclerosis **(MS)**

Common-Method Variance **(CMV)**

Trial to Reduce cardiovascular Events with Aranesp Therapy **(TREAT)**

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Abstract

Background: Fatigue has been under-investigated in stable kidney transplant recipients (KTRs). The objectives of this study were to investigate the nature, severity, prevalence and clinical awareness of fatigue in medically stable KTRs, examine the impact of fatigue on quality of life (QoL), and explore the underlying causes of post-transplant fatigue.

Methods: This single-centre cross-sectional study enrolled 106 stable KTRs. Multi-Dimensional Fatigue Inventory (MFI-20) was used to measure 5 fatigue dimensions: General Fatigue (GF), Physical Fatigue (PF), Reduced Activity (RA), Reduced Motivation (RM), Mental Fatigue (MF). Clinical awareness of fatigue was determined by reviewing medical records. QoL was assessed by Medical Outcomes Study Short Form (SF-36) Questionnaire. Demographic, clinical, psychosocial and behavioural parameters were evaluated as fatigue predictors.

Results: Fatigue was found in 59% of KTRs. Only 13% had this symptom documented in medical records. Fatigue in KTRs was in the same range as chronically unwell patients, with PF, RA and RM approached levels observed in chronic fatigue syndrome. All fatigue dimensions significantly and inversely correlated with QoL ($p<0.001$ for all associations). Demographic predictors were male, older age and non-Caucasian ethnicity ($p\leq0.05$ for all associations). Clinical predictors included elevated hsCRP (inflammation), decreased eGFR (graft dysfunction), and reduced lean tissue index ($p\leq0.05$ for all associations). Psychosocial and behavioural predictors were inferior sleep quality, anxiety and depression ($p<0.01$ for all associations).

Conclusions: Fatigue is common and pervasive in clinically stable KTRs. It is strongly associated with reduced QoL. This study identified modifiable fatigue predictors, and sets the scene for future interventional studies.

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Introduction

Fatigue is an important patient-reported outcome in many medical conditions (1, 2) and involves physical (e.g. feeling exhausted and tired), cognitive (e.g. impaired concentration), emotional (e.g. lack of motivation) and functional components (3). It is often medically unexplained (4) and persistent (2), and interferes with an individual's ability to function in important roles (e.g. work, family, social life, self-care) (5). As a corollary, fatigue can have a major negative impact upon quality of life (QoL) (6).

In chronic dialysis patients, fatigue is frequently reported as a pervasive and distressing symptom (7-9). For many of these patients, kidney transplantation (KT) is the preferred modality of renal replacement therapy (10). KT increases long term survival (10), improves QoL (11), demonstrates cost benefits (12), and results in enhanced sense of well-being. Consequently, it might be assumed that fatigue no longer feature as a major problem following KT, but in fact there has been very little research to either confirm or refute this assumption. Only one study has specifically examined fatigue following transplantation (13), noting the symptom was reported in 59% of kidney transplant recipients (KTRs) and that it negatively impacted on virtually every aspect of the QoL (13). Poor sleep quality, mood disturbance and raised body mass index were identified as significant predictors for post-transplant fatigue (13). However, other potentially modifiable contributors to fatigue such as body composition, inflammation, renal function, and other biochemical markers were not examined and warrant further investigation.

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Greater insight into fatigue severity, its impact on QoL, and its possible underlying causes are all pre-requisites for developing interventions to combat this symptom. In addition, it is also important to know the extent to which clinicians are aware of the problem. Therefore, the objectives of this study were to determine the nature, severity, prevalence and clinical awareness of post-transplant fatigue in a clinically-stable prevalent kidney transplant cohort. Additionally, this study aimed to examine the impact of this symptom upon QoL, and to explore the predictors of post-transplant fatigue.

Results

Patient characteristics

The characteristics of the studied population are shown in **Table 1**.

Relationship between different domains of fatigue

The correlations between different domains of fatigue are shown in **Table 2**.

Nature, severity and prevalence of fatigue

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The nature and severity of fatigue are shown in **Table 3**, alongside normative data obtained from Lin's study (14). Comparison of the Multi-Dimensional Fatigue Inventory (MFI-20) subscales indicated that significant differences were found between the following dimensions: General Fatigue [GF] and Reduced Activity [RA] (p=0.002); GF and Reduced Motivation [RM] (p<0.001); GF and Mental Fatigue [MF] (p<0.001); Physical Fatigue [PF] and RA (p=0.002); PF and RM (p<0.001); PF and MF (p<0.001); RA and RM (p<0.001); RA and MF (p<0.001). The differences between the following dimensions were not statistically significant: GF and PF (p=0.881); RM and MF (p=0.801). In summary, physical aspects of fatigue (GF and PF) in KTRs were scored significantly higher than behavioural, emotional and cognitive aspects of fatigue (RA, RM and MF). Overall, the mean MFI-20 scores in KTRs exceeded the mean scores found in the general population and were comparable to the mean scores reported by chronically unwell patients. In fact, the mean scores for PF, RA and RM approached the mean values reported by Chronic Fatigue Syndrome (CFS) patients.

Based on the dichotomous classification of fatigue (≥ upper 95th percentile for the general population, see **Materials and Methods**), a total of 63 patients (59%) reported fatigue on at least one MFI-20 subscale. Of these 63 patients, 24% experienced GF, 38% displayed PF, 35% demonstrated RA, 29% indicated RM, and 25% revealed MF. Importantly, only 8 patients (13%) had complaints of fatigue documented in medical records.

Fatigue and quality of life

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As shown in **Table 4,** all dimensions of fatigue (GF, PF, RA, RM and MF) were significantly and inversely correlated with all aspects of QoL including SF-36 physical health, SF-36 mental health and SF-36 total score. To exclude the confounding effect of the SF-36 "energy and vitality" subscale, which is a general measure of fatigue within the SF-36 (15), results were reanalysed after removal of this subscale, results were comparable after this exclusion (shown in parentheses in **Table 4**).

Factors predicting dimensions of fatigue

Linear regression analyses, to identify predictors of each fatigue dimension, were performed in 3 stages. First, univariate analyses tested the predictive value of each parameter individually. Second, multivariate analyses tested the independent prediction of all parameters. Third, the analysis was adjusted for anxiety, depression, and sleep quality, thereby focusing on clinical, anthropometric and laboratory parameters.

General Fatigue

The univariate analyses are shown in **SDC, Table 5a**. In multivariate analysis, only depression (β=2.8; 95% CI=1.9, 3.7; p<0.001) and inferior sleep quality (β=1.1; 95% CI=0.2, 1.9; p=0.01) were independently associated with GF (**SDC, Figure 1** and **SDC, Figure 2**). Repeating the multivariate analysis excluding Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI) revealed that increasing time post-transplantation (β=0.6; 95% CI=0.0, 1.1; p=0.04), inflammation (β=1.8; 95% CI=0.3, 3.3;

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p=0.02), and renal dysfunction (*β*=-0.4; 95% CI=-0.8, 0.0; *p*=0.04) were independently associated with increasing fatigue.

Physical Fatigue

The univariate analyses are shown in **SDC, Table 5b**. In the multivariate model, depression (*β*=3.2; 95% CI=2.3, 4.1; *p*<0.001), renal dysfunction (*β*=-0.7; 95% CI=-1.4, -0.5; *p*<0.001; **SDC, Figure 3**), inflammation (*β*=1.4; 95% CI=0.0, 2.7; *p*=0.05), reduced LTI (*β*=-0.5; 95% CI=-0.8, -0.3; *p*<0.001; **SDC, Figure 4**) and male (*β*=2.4; 95% CI=0.9, 4.0; *p*=0.003) were independently associated with PF. Repeating the multivariate analysis excluding HADS and PSQI showed that renal dysfunction (*β*=-0.8; 95% CI=-1.2, -0.4; *p*<0.001), inflammation (*β*=2.6; 95% CI=1.0, 4.1; *p*=0.002), increasing time post-transplantation (*β*=0.7; 95% CI=0.2, 1.3; *p*=0.01), reduced LTI (*β*=-0.6; 95% CI=-0.9, -0.3; *p*<0.001), and male (*β*=3.1; 95% CI=1.2, 5.0; *p*=0.001) were independently associated with PF.

Reduced Activity

The univariate analyses are shown in **SDC, Table 5c.** In the multivariate model, depression (*β*=3.4; 95% CI=1.9, 3.7; *p*<0.001), inflammation (*β*=2.7; 95% CI=1.2, 4.1; *p*<0.001; **SDC, Figure 5**), and increasing age (*β*=0.7; 95% CI=0.2, 1.1; *p*=0.003) were independent predictors for RA. Following exclusion of HADS and PSQI, inflammation (*β*=3.8; 95% CI=2.2, 5.4; *p*<0.001), increasing comorbidity (*β*=3.4; 95% CI=1.0, 5.7; *p*=0.006), increasing time post-transplantation (*β*=0.6; 95% CI=0.0, 1.2; *p*=0.04), and increasing age (*β*=0.6; 95% CI=0.2, 1.1; *p*=0.04) were independently associated with RA.

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Reduced Motivation

The univariate models are shown in **SDC, Table 5d.** In the multivariate analysis, depression (Odds Ratio = 1.40; CI=1.30, 1.52; $p<0.001$), renal dysfunction (Odds Ratio = 0.96; CI=0.93, 1.00; $p=0.03$), and reduced LTI (Odds Ratio = 0.98; CI=0.96, 1.00; $p=0.05$) were associated with RM independently. Following exclusion of HADS and PSQI, increasing time post-transplantation (Odds Ratio = 1.07; CI=1.01, 1.13; $p=0.02$), renal dysfunction (Odds Ratio = 0.95; CI=0.92, 0.99; $p=0.02$), and inflammation (Odds Ratio = 1.22; CI=1.05, 1.43; $p=0.01$) were independent predictors for RM.

Mental Fatigue

Finally, the univariate analyses predicting MF are shown in **SDC, Table 5e.** In the multivariate model, only anxiety was independently associated with fatigue (Odds Ratio = 1.36; CI=1.24, 1.49; $p<0.001$; **SDC, Figure 6**). A borderline effect of ethnicity was found (Odds Ratio = 1.42; CI=1.01, 1.99; $p=0.05$). When the multivariate analysis was repeated excluding the HADS and PSQI results, no predictor variables retained statistical significance.

Discussion

This study aimed to investigate the nature, severity, prevalence and clinical awareness of post-transplant fatigue, determine the association between fatigue and QoL, and identify main predictors of post-transplant fatigue. The results revealed that in clinically stable KTRs without evidence of intercurrent disease, fatigue is common, severe, and clinically under-

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appreciated. It has a close association with inferior QoL. These results confirm and significantly extend the findings of the single previous study on post-transplant fatigue (13), and advances understanding of the possible determinants of fatigue by showing associations with anthropometric and clinical variables not previously evaluated. Depression, anxiety, inferior sleep quality, inflammation, reduced muscle mass, and renal dysfunction were identified as risk factors, forming potential targets for future interventional studies.

The significant correlations between different domains of fatigue suggest that treatment of behavioural, emotional and cognitive aspects of fatigue may improve physical aspects of fatigue, or vice versa. However, a recent study provides experimental evidence that mental fatigue limits exercise tolerance in humans via higher perception of effort rather than cardiorespiratory and musculoenergetic mechanisms (16), implying that the overall focus of fatigue management should be on the behavioural, emotional and cognitive aspects.

Compared to normative data from healthy population (14, 17), KTRs suffer from higher levels of fatigue on all dimensions. In comparison to normative data from Lin (14), fatigue levels in KTRs were similar to "chronically unwell" patients, defined as having chronic ($\geq$ 6 months) unwellness with or without fatigue, but not meeting criteria for CFS (14). Indeed, severity in certain domains, such as PF, RA and RM, approached that of CFS (14), further highlighting the burden of fatigue in KTRs. Of note, the level of MF was higher in KTRs compared to cancer patients with mild anaemia undergoing chemotherapy (17), and chronic heart failure patients with and without anaemia (18). Also, KTRs suffer from higher levels of PF, RA and RM compared to cancer patients without anaemia (17). Physical aspects of

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fatigue outweighed behavioural, emotional and cognitive aspects, resembling findings in liver transplant recipients (19).

Using a dichotomous fatigue definition, 24-38% of participants reported fatigue in at least one of the five dimensions, and 59% in any dimension. This prevalence is comparable to that found by Rodrigue (13) using the one-dimensional "Fatigue Symptom Inventory". Despite the high prevalence, only 13% of patients had fatigue documented in medical records prior to participation in this study, suggesting that this symptom is either under-reported or under-acknowledged. Furthermore, the close correlation between all fatigue domains and QoL resonates with the clinical and social relevance of this symptom.

The assessment of multiple domains of fatigue, and the measurement from the clinically validated HADS extends the findings of Rodrigue (13) where fatigue severity significantly correlated with a composite mood score incorporating depression, vigour, anger, confusion, anxiety and fatigue itself. The current study highlights the specific, independent importance of depression as a risk factor for all dimensions of fatigue except for MF. This exception is surprising as previous study on multiple sclerosis (MS) related fatigue found that depression was related to MF (20, 21). However, depression and MF can occur independently or simultaneously (22), this phenomenon has been demonstrated in stroke patients (22) . Many symptoms for depression and MF overlap, but the core symptoms are different. The lack of association in this study may be explained by the distinction between the core symptoms. Depression is an illness or mood disorder with a variety of symptoms, the most defining being an inexplicable, enduring feeling of sadness, and loss of positive effect (23). The collective symptoms may not manifest as MF, which is a psychobiological state caused by

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prolonged periods of demanding cognitive activity such as concentration, attention and increased mental load (16). In MF, mental effort can only be sustained for a short time-frame, and recovery period is disproportionally long (22). Accompanying symptoms include irritability, sensitivity to stress, concentration difficulties, and emotional instability (22). Anxiety was a significant predictor for MF, similar to other chronic conditions such as MS (21). KTRs are subjected to several mental challenges, including fears about transplant rejection and the necessity to adhere to a complex regimen of immunosuppression therapy that may generate distressing side effects (24). To an extent, the unpredictable clinical course post-transplantation is reminiscent of the relapsing and remitting nature of MS. While acknowledging the limitations of cross-sectional data to make causal inferences, the present results are in line with evidence showing that psychological interventions addressing disease-related anxiety and depression *per se* may yield added benefit in modifying fatigue.

While inferior sleep quality may intuitively be expected to have a pervasive and broad effect on multiple aspects of fatigue (13), a significant association was only observed for the GF dimension. This finding suggests that mere sleep difficulties do not explain a large spectrum of the fatigue complaints in KTRs, and interventions aiming to improve sleep quality may have limited effect on fatigue.

An important caveat with the interpretation of the associations between self-reported data, such as depression, sleep difficulties and symptoms of fatigue is that common-method variance (CMV) may partly drive the observed associations, and may account for 25% of shared variance (25). In CMV, patients high in negative affect (i.e. negative mood) perceive, remember and report more physical and psychological symptoms, and report those symptoms

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to be more severe than patients with a less negative mood (26). Additionally, individual items on questionnaires measuring fatigue, depression or sleep problems tend to show conceptual overlap, which further enhances co-variation. While these would not render self-reports unimportant, and neither would refute that sleep and depression may have strong bidirectional links with fatigue, potential interpretational difficulties may result. Therefore, this study's detailed anthropometric and biochemical data represents an important extension of the previous study in the field (13). When multivariate regression analysis excluded adjustment for mood and sleep, reduced LTI, renal impairment and inflammation were identified as potentially reversible predictors.

The association between inflammation and fatigue is particularly notable as the studied cohort consisted of clinically stable KTRs, without overt evidence of ongoing acute or chronic inflammatory conditions. Evidence from studies of healthy volunteers, elderly populations and other disease groups have shown that inflammatory cytokines possess potent neurological effects and are mediators of fatigue (13, 27-30). Modifying inflammation may therefore represent an attractive target in future studies.

The independent association between physical fatigue and reduced LTI is intuitively plausible, but not previously reported in KTRs. It replicates results from cancer-related fatigue (31), and fatigue associated with end-stage renal disease on haemodialysis (32, 33). Reduced muscle mass coupled with increased fat mass ("sarcopenic obesity") is a common characteristic of body composition following KT (34). Despite significant univariate associations between FTI and different dimensions of fatigue (GF, PF, RA and RM), this relationship did not hold when adjusted for inflammation, suggesting inflammation as the

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driver for fatigue, rather than adiposity per se. This study advances understanding from Rodrigue (13) where raised BMI (a proxy for fat mass) was identified as a predictor of fatigue, but detailed anthropometric and inflammatory evaluation was not undertaken. However, it is possible that the systemic low-grade inflammation present in obesity triggers adipocyte release of pro-inflammatory cytokines (35), this in turn accelerates muscle catabolism (36), leading to muscle wasting (36). The current study suggests that lifestyle interventions with a strong focus on increased physical activity and dietary modification aiming to reverse this phenotype should be valuable for patients displaying symptoms of fatigue. Apart from promoting favourable changes in body composition, lifestyle modification is particularly important in light of the inverse associations between all domains of fatigue and SF-36 physical health subscale, which is a representation of self-perceived physical functioning. Recent studies reported that self-perceived physical functioning is significantly and positively correlated with physical activity level (37, 38). Although physical activity level was not measured in the current study, this finding suggests that striving to be physically active enhances functional capacity and improves self-perception of physical functioning, leading to improved fatigue and quality of life.

Although fatigue is a common and important symptom for patients on dialysis (7, 8), the present results show, for the first time, a relationship between allograft dysfunction and physical fatigue in KTRs. Clinical strategies exist to improve allograft function (39) and fatigue may represent an important patient-reported outcome in future interventional studies.

Other non-modifiable, but important, risk factors for varying domains of fatigue included male, older age, ethnicity, comorbidity, and increasing time post-transplantation.

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The lack of association between haemoglobin level and fatigue is unsurprising as the results from the TREAT study (Trial to Reduce cardiovascular Events with Aranesp Therapy) (40) only showed a small improvement in fatigue with haemoglobin normalisation, using recombinant erythropoietin in non-transplant, diabetic, chronic kidney disease.

The use of immunosuppressive medication was not associated with fatigue in KTRs. Of relevance, no link between immunosuppression and fatigue was seen in previous studies of liver transplant recipients (19) and KTRs (13).

This study has limitations that should be acknowledged. It is a single-centre study with a small sample size. The progression and regression of fatigue over time could not be evaluated due to the study design of cross-sectional nature. The results may not be representative of "sicker" patients within the transplanted population. It is recognised that hyperparathyroidism occurs in a substantial proportion of KTRs (17%) (41), with fatigue as a possible manifestation. Unfortunately, serum parathyroid hormone concentrations were not routinely measured in this study.

Whilst kidney transplantation is associated with a variety of benefits compared with dialysis, this study shows that fatigue remains a common and relevant problem in otherwise stable KTRs. As the medical complexity of KTRs increases, it is important not to lose sight of important patient-reported outcomes such as fatigue. This study demonstrates potential

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targets for intervention, and future research should focus on evaluating the effectiveness and impact of such interventions upon fatigue and QoL.

Materials and Methods

Participants and study design

Stable KTRs beyond 1 year post-transplantation, with stable graft function (<10% increase in serum creatinine over preceding 6 months) were recruited to this cross-sectional study from the renal transplant outpatient clinic at Queen Elizabeth Hospital Birmingham UK, between April 2010 and April 2012. Exclusion criteria included episodes of acute rejection within the last 6 months, evidence of sepsis in the last 6 weeks, known active malignancy or chronic infection, preceding diagnosis of psychiatric disorder or chronic fatigue syndrome, and history of thyroid disease or adrenal insufficiency.

Of 114 eligible patients approached, n=6 refused to participate and n=2 did not attend the research visit. Reasons for declining entry were work commitment (n=4) and participation in other studies (n=2). The study was approved by the local research ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients attended the research visit following a 10-hour overnight fast. The order of tests was standardised. A fasting blood sampling was taken, followed by a light breakfast before bio-

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impedance body composition assessment, and self-completion of questionnaires under supervision of the researcher (see below).

Fatigue measurement

Severity and nature of fatigue were determined using the MFI-20, which is a 20-item self-report questionnaire that measures fatigue in 5 primary dimensions: General Fatigue (GF); Physical Fatigue (PF); Reduced Activity (RA); Reduced Motivation (RM); Mental Fatigue (MF). The physical aspects of fatigue are captured by GF and PF; and the behavioural, emotional and cognitive aspects of fatigue are represented by RA, RM, and MF (42) (see **SDC, Materials and Methods** for scoring and description of MFI-20).

A consensus definition for clinically meaningful fatigue is lacking. In this study, KTRs were considered fatigued if scores for any dimension was ≥ upper 95th percentile for the general population as reported by Lin (14) (GF ≥ 15; PF ≥ 14; RA ≥ 12; RM ≥ 12; MF ≥ 13). The present data were also compared with two other clinical groups, similarly derived from Lin (14), namely patients with CFS and patients with other chronic (> 6 months) diseases.

Reporting of fatigue by clinicians was assessed by retrieving medical records for the 4 clinic visits prior to participation in this study (see **SDC, Materials and Methods** for explanation of medical record retrieval).

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Quality of life assessment

QoL was assessed using the Medical Outcomes Study Short Form 36 (SF-36) questionnaire, which generates the total score for QoL, as well as physical health and mental health sub-scores (see **SDC, Materials and Methods** for scoring and description of SF-36).

Factors associated with fatigue

Demographics and clinical parameters

Age, gender, marital status, ethnicity, and time post-transplantation were collected from patients' medical records. Smoking status (never smoked, current smoker, ex-smoker) and alcohol intake (units per week) were collected by questionnaire. Co-morbidity was assessed by Index of Co-Existing Disease (ICED), using the algorithm described by the Hemodialysis (HEMO) Study (43), with data extracted from patients' medical records. Presence of diabetes, either pre-transplantation (pre-DM) or new onset diabetes after transplantation (NODAT), prior acute rejection episodes, and immunosuppressive medication usage were retrieved from patients' medical records.

Laboratory parameters

Fasting blood sample was taken for analysis of high sensitive C-reactive protein (hsCRP), haemoglobin (Hb) and estimated glomerular filtration rate (eGFR) derived using the 4-variable modification of diet in renal disease equation (44).

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Body composition

Body composition was assessed by multi-frequency bio-impedance measurement, using the body composition monitor to provide values for Lean Tissue Index (LTI) and Fat Tissue Index (FTI) (see **SDC, Materials and Methods** for explanation of bio-impedance measurement).

Self-reported outcome measures

Anxiety and Depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (45). Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (46). See **SDC, Materials and Methods** for scoring and description of HADS and PSQI.

Statistical analysis

Statistical analysis was performed using STATA. Results are presented as mean ± standard deviation or median (interquartile range). Independent sample *t*-tests were used to compare continuous variables, and Pearson correlation coefficients to assess relationship.

Linear regression analysis was used to determine predictor variables associated with different domains of fatigue. The analyses were performed in two stages. Initially, the effect of each variable was examined in a series of univariate analyses. Subsequently, the joint effect of variables was examined in a multivariate analysis, using a backwards selection procedure to derive the final model. A type 1 error rate ≤5% ($p \leq 0.05$) was considered significant. Results

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for GF, PF and RA revealed normal distributions and were analysed on the original scale of measurement. Results for RM and MF demonstrated positively skewed distributions and underwent logarithmic transformation prior to analysis. In the multivariate regression analyses, only the explanatory variables with univariate *p*-values of <0.20 were included. The figures reported in **SDC, Tables 5a, 5b, 5c, 5d and 5e**, were regression coefficients or odds ratios, and their corresponding confidence intervals. The regression coefficients and odds ratios describe the change in fatigue for the described increase (or category) of the predictor variable.

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http://dx.doi.org/10.1097/TP.0b013e3182a2e88b

References

1. Stone P, Richards M and Hardy J: Fatigue in patients with cancer. European journal of cancer (Oxford, England : 1990) 34: 1670-1676, 1998
2. Donovan KA, Jacobsen PB, Small BJ, Munster PN and Andrykowski MA: Identifying Clinically Meaningful Fatigue with the Fatigue Symptom Inventory. Journal of pain and symptom management 36: 480-487, 2008
3. Dittner AJ, Wessely SC and Brown RG: The assessment of fatigue: A practical guide for clinicians and researchers. Journal of psychosomatic research 56: 157-170, 2004
4. Skapinakis P, Lewis G and Mavreas V: Temporal Relations Between Unexplained Fatigue and Depression: Longitudinal Data From an International Study in Primary Care. Psychosomatic Medicine 66: 330-335, 2004
5. Ream E and Richardson A: Fatigue: a concept analysis. International Journal of Nursing Studies 33: 519-529, 1996
6. Hjollund N, Andersen J and Bech P: Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. Health and Quality of Life Outcomes 5: 12, 2007
7. Jhamb M, Weisbord SD, Steel JL and Unruh M: Fatigue in Patients Receiving Maintenance Dialysis: A Review of Definitions, Measures, and Contributing Factors. American Journal of Kidney Diseases 52: 353-365, 2008
8. Murtagh FEM, Addington-Hall J and Higginson IJ: The Prevalence of Symptoms in End-Stage Renal Disease: A Systematic Review. Advances in chronic kidney disease 14: 82-99, 2007
9. Ramkumar N, Beddhu S, Eggers P, Pappas LM and Cheung AK: Patient preferences for in-center intense hemodialysis. Hemodialysis International 9: 281-295, 2005
10. Wolfe RA, Ashby VB, Milford EL, et al.: Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. New England Journal of Medicine 341: 1725-1730, 1999
11. McDonald SP and Russ GR: Survival of recipients of cadaveric kidney transplants compared with those receiving dialysis treatment in Australia and New Zealand, 1991–2001. Nephrology Dialysis Transplantation 17: 2212-2219, 2002
12. Machnicki G, Seriai L and Schnitzler MA: Economics of transplantation: a review of the literature. Transplantation reviews (Orlando, Fla) 20: 61-75, 2006
13. Rodrigue JR, Mandelbrot DA, Hanto DW, Johnson SR, Karp SJ and Pavlakis M: A cross-sectional study of fatigue and sleep quality before and after kidney transplantation. Clinical Transplantation 25: E13-E21, 2011
14. Lin J-M, Brimmer D, Maloney E, Nyarko E, BeLue R and Reeves W: Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. Popul Health Metrics 7: 18, 2009
15. Brown L, Kroenke K, Theobald D and Wu J: Comparison of SF-36 vitality scale and Fatigue Symptom Inventory in assessing cancer-related fatigue. Support Care Cancer 19: 1255-1259, 2011
16. Marcora SM, Staiano W and Manning V: Mental fatigue impairs physical performance in humans. Journal of Applied Physiology 106: 857-864, 2009
17. Holzner B, Kemmler G, Greil R, et al.: The impact of hemoglobin levels on fatigue and quality of life in cancer patients. Annals of Oncology 13: 965-973, 2002
18. Falk K, Swedberg K, Gaston-Johansson F and Ekman I: Fatigue and anaemia in patients with chronic heart failure. European Journal of Heart Failure 8: 744-749, 2006
19. van den Berg-Emons R, van Ginneken B, Wijffels M, et al.: Fatigue is a major problem after liver transplantation. Liver Transplantation 12: 928-933, 2006
20. Schreurs KMG, de Ridder DTD and Bensing JM: Fatigue in multiple sclerosis: Reciprocal relationships with physical disabilities and depression. Journal of psychosomatic research 53: 775-781, 2002

21. Ford H, Trigwell P and Johnson M: The nature of fatigue in multiple sclerosis. Journal of psychosomatic research 45: 33-38, 1998
22. Johansson B and Rönnbäck L: Mental fatigue and cognitive impairment after an almost neurological recovered stroke. ISRN Psychiatry 2012: 1-7, 2012
23. Robertson R, Robertson A, Jepson R and Maxwell M: Walking for depression or depressive symptoms: A systematic review and meta-analysis. Mental Health and Physical Activity 5: 66-75, 2012
24. Crone C and Gabriel G: Treatment of Anxiety and Depression in Transplant Patients: Pharmacokinetic Considerations. Clinical Pharmacokinetics 43 361-394, 2004
25. Podsakoff PM, MacKenzie SB, Lee J-Y and Podsakoff NP: Common method biases in behavioral research: A critical review of the literature and recommended remedies. Journal of Applied Psychology 88: 879-903, 2003
26. Watson D and Pennebaker JW: Health complaints, stress, and distress: Exploring the central role of negative affectivity. Psychological Review 96: 234-254, 1989
27. Visser M, Pahor M, Taaffe DR, et al.: Relationship of Interleukin-6 and Tumor Necrosis Factor-α With Muscle Mass and Muscle Strength in Elderly Men and Women. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 57: M326-M332, 2002
28. Schubert C, Hong S, Natarajan L, Mills P and Dimsdale J: The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. Brain Behav Immun 21 413-427, 2007
29. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW and Irwin MR: Inflammatory Biomarkers for Persistent Fatigue in Breast Cancer Survivors. Clinical Cancer Research 12: 2759-2766, 2006
30. Meyers CA, Albitar M and Estey E: Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer 104: 788-793, 2005
31. Kilgour R, Vigano A, Trutschnigg B, et al.: Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. Journal of Cachexia, Sarcopenia and Muscle 1: 177-185, 2010
32. Cheema B: Review article: Tackling the survival issue in end-stage renal disease: time to get physical on haemodialysis. Nephrology Dialysis Transplantation 13: 560-569, 2008
33. Sawant A, Garland S, House A and Overend T: Morphological, electrophysiological, and metabolic characteristics of skeletal muscle in people with end-stage renal disease: a critical review. Physiother Can 63: 355-376, 2011
34. Schütz T, Hudjetz H, Roske A-E, et al.: Weight gain in long-term survivors of kidney or liver transplantation—Another paradigm of sarcopenic obesity? . Nutrition (Burbank, Los Angeles County, Calif) 28: 378-383, 2012
35. Shoelson S, Herrero L and Naaz A: Obesity, Inflammation, and Insulin Resistance. Gastroenterology 132: 2169-2180, 2007
36. Schrager M, Metter E, Simonsick E, et al.: Sarcopenic obesity and inflammation in the InCHIANTI study. Journal of applied physiology (Bethesda, Md : 1985) 102: 919-925, 2007
37. Fontaine KR, Conn L and Clauw DJ: Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. Arthritis Research & Therapy 12: R55, 2010
38. Szeklicki R, Osiński W, Maciaszek J, Stemplewski R and Salamon A: Correlations between habitual physical activity and self-perceived functional fitness, self-sufficiency fitness and health among men over 60 years old. HUMAN MOVEMENT 14: 27-34, 2013
39. Moore J, Middleton L, Cockwell P, et al.: Calcineurin Inhibitor Sparing With Mycophenolate in Kidney Transplantation: A Systematic Review and Meta-Analysis. Transplantation 87: 591-605 510.1097/TP.1090b1013e318195a318421, 2009
40. Lewis EF, Pfeffer MA, Feng A, et al.: Darbepoetin Alfa Impact on Health Status in Diabetes Patients with Kidney Disease: A Randomized Trial. Clinical Journal of the American Society of Nephrology 6: 845-855, 2011

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41. Evenepoel P, Claes K, Kuypers D, Maes B, Bammens B and Vanrenterghem Y: Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. Nephrology Dialysis Transplantation 19: 1281-1287, 2004
42. Wong CJ, Goodridge D, Marciniuk DD and Rennie D: Fatigue in patients with COPD participating in a pulmonary rehabilitation program. International Journal of Chronic Obstructive Pulmonary Disease 5: 319–326, 2010
43. Miskulin DC, Athienites NV, Yan G, et al.: Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. Kidney Int 60: 1498-1510, 2001
44. Levey AS, Coresh J, Greene T, et al.: Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clinical Chemistry 53: 766-772, 2007
45. Zigmond A and Snaith R: The hospital anxiety and depression scale. Acta Psychiatr Scand 67: 361-370, 1983
46. Backhaus J, Junghanns K, Broocks A, Riemann D and Hohagen F: Test–retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. Journal of psychosomatic research 53: 737-740, 2002

Post-print, cite as Chan, W.L.W., Bosch, J.A., Jones, D., Kaur, O., McLean, A., McTernan, P.G., Harper, L., Phillips, A.C., Borrows, R. (2013). Predictors and consequences of fatigue in prevalent kidney transplant patients. Transplantation, 96, 987-994. IF 3.78
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Table 1: Population Characteristics

	Characteristics
Sample size	n = 106
†**Mean age**	51 ± 14 years
Gender	56% Male; 44% Female
Marital status	Single 21%; Married 71%; Divorced/Widowed 8%
Immunosuppressive medication usage	
Calcineurin inhibitor	89% (55% Tacrolimus, 34% Cyclosporin)
Adjunctive antiproliferatives	87% (58% Mycophenolate Mofetil, 29% Azathioprine)
Prednisolone	74%
Dosage of immunosuppressive medications	
‡Median dose of Tacrolimus	4.0 (2.5-6.0) mg/day
‡Median dose of Cyclosporin	150 (150-200) mg/day
†Mean dose of Mycophenolate Mofetil	987 ± 392 mg/day
†Mean dose of Azathioprine	77 ± 36 mg/day
†Mean dose of Prednisolone	5.2 ± 1.0 mg/day
***Ethnicity**	
Caucasian	76%
Afro-Caribbean	7%
Asian	15%
Other	2%
‡**Median time post transplantation**	6.5 (3.0-14.0) years
‡**Median alcohol intake per week**	0.0 (0.0-3.0) units
Smoking status	
Never smoked	63%
Current smoker	7%
Ex-smoker	30%
†**Mean ICED score (co-morbidity)**	2.1 ± 0.4
Score = 1	2%
Score = 2	85%
Score = 3	13%
†**Mean Hb**	12.6 ± 1.6 g/dl
‡**Median hsCRP**	2.5 (1.0-4.9) mg/l
†**Mean eGFR**	43.9 ± 18.5 ml/min
Body composition	
†Mean lean tissue index (LTI)	13.9 ± 3.0 kg/m^2
†Mean fat tissue index (FTI)	14.2 ± 6.2 kg/m^2
HADS	
‡Median anxiety score	6.0 (2.5-9.5)
‡Median depression score	3.0 (1.0-7.0)
PSQI	
†Mean global score	7.2 ± 4.1

†Normally distributed data, results expressed as mean ± SD. ‡Non-normally distributed data, results expressed as median (Interquartile Range). *For the purpose of the statistical analysis, the ethnicity of 2% of patients classified as "Other" was grouped as "Caucasian". **For the purpose of the statistical analysis, the Index of Co-Existent Disease (ICED) scores were arranged into 2 categories (≤2 versus >2, 87% and 13% of patients respectively).

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Table 2: Correlation between different domains of fatigue

Pearson correlation (*r*); *p*-value for each correlation

	General Fatigue (GF)	**Physical Fatigue (PF)**	**Reduced Activity (RA)**	**Reduced Motivation (RM)**	**Mental Fatigue (MF)**
General Fatigue (GF)		*r*=0.74; *p*<0.001	*r*=0.68; *p*<0.001	*r*=0.65; *p*<0.001	*r*=0.46; *p*<0.001
Physical Fatigue (PF)	*r*=0.74; *p*<0.001		*r*=0.76; *p*<0.001	*r*=0.69; *p*<0.001	†*r*=0.34; *p*<0.001
Reduced Activity (RA)	*r*=0.68; *p*<0.001	*r*=0.76; *p*<0.001		*r*=0.62; *p*<0.001	*r*=0.32; *p*=0.001
Reduced Motivation (RM)	*r*=0.65; *p*<0.001	*r*=0.69; *p*<0.001	*r*=0.62; *p*<0.001		*r*=0.46; *p*<0.001
Mental Fatigue (MF)	*r*=0.46; *p*<0.001	*r*=0.34; *p*<0.001	*r*=0.32; *p*=0.001	*r*=0.46; *p*<0.001	

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Table 3: Nature and Severity of Fatigue

Mean Fatigue Score ± SD by Dimensions

	Transplant Patients	**Healthy Population†**	**Chronically Unwell Patients†**	**Chronic Fatigue Syndrome-like Patients†**
General Fatigue (GF)	11.78 ± 4.05	8.42 ± 3.59	12.84 ± 3.84	16.38 ± 2.73
Physical Fatigue (PF)	11.73 ± 4.74	7.77 ± 3.36	10.39 ± 3.76	13.63 ± 3.79
Reduced Activity (RA)	10.69 ± 4.70	6.76 ± 2.67	9.06 ± 3.75	11.32 ± 4.37
Reduced Motivation (RM)	9.36 ± 3.61	6.82 ± 2.91	9.29 ± 3.35	11.95 ± 3.53
Mental Fatigue (MF)	9.67 ± 4.54	7.23 ± 3.07	10.98 ± 4.00	13.77 ± 3.77

†Original unpublished normative data provided by Lin et al (14).

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Table 4: Association between Fatigue and Quality of Life

	SF-36 Physical Health	**SF-36 Mental Health**	**SF-36 Total Score**
General Fatigue (GF)	†r=-0.68; p<0.001 *(r=-0.62; p<0.001)	†r=-0.70; p<0.001 *(r=-0.63; p<0.001)	†r=-0.68; p<0.001 *(r=-0.64; p<0.001)
Physical Fatigue (PF)	†r=-0.78; p<0.001 *(r=-0.74; p<0.001)	†r=-0.71; p<0.001 *(r=-0.65; p<0.001)	†r=-0.74; p<0.001 *(r=-0.72; p<0.001)
Reduced Activity (RA)	†r=-0.72; p<0.001 *(r=-0.69; p<0.001)	†r=-0.67; p<0.001 *(r=-0.62; p<0.001)	†r=-0.71; p<0.001 *(r=-0.68; p<0.001)
Reduced Motivation (RM)	†r=-0.66; p<0.001 *(r=-0.64; p<0.001)	†r=-0.69; p<0.001 *(r=-0.66; p<0.001)	†r=-0.69; p<0.001 *(r=-0.68; p<0.001)
Mental Fatigue (MF)	†r=-0.33; p<0.001 *(r=-0.29; p<0.01)	†r=-0.49; p<0.001 *(r=-0.48; p<0.001)	†r=-0.42; p<0.001 *(r=-0.41; p<0.001)

†Correlation and *p*-value derived from comparisons between all domains of fatigue and all SF-36 subscales in the analysis.
*Correlation and *p*-value in parentheses derived from comparisons between all domains of fatigue and SF-36 excluding "energy and vitality" subscale in the analysis.