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ORIGINAL ARTICLE

Cardiovascular, muscular and perceptual contributions to physical fatigue in prevalent kidney transplant recipients

Winnie Chan,[1,2,3] David Jones,[4] Jos A. Bosch,[2,5] Jamie McPhee,[4] Nicola Crabtree,[6] Philip G. McTernan,[7] Okdeep Kaur,[1] Nicholas Inston,[1] Sue Moore,[1] Andrew McClean,[1] Lorraine Harper,[1] Anna C. Phillips[2] and Richard Borrows[1,8]

1 Department of Nephrology & Kidney Transplantation, Queen Elizabeth Hospital Birmingham, Birmingham, UK
2 School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK
3 Department of Nutrition & Dietetics, Queen Elizabeth Hospital Birmingham, Birmingham, UK
4 School of Healthcare Science, Manchester Metropolitan University, Manchester, UK
5 Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands
6 Department of Nuclear Medicine, Queen Elizabeth Hospital Birmingham, Birmingham, UK
7 Division of Metabolic and Vascular Health, Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry, UK
8 Translational Inflammation Research, University of Birmingham, Birmingham, UK

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Correspondence
Dr Richard Borrows, Department of Nephrology & Kidney Transplantation, Area 5, Level 7, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, UK.
Tel.: +44 (0) 121 371 6099;
fax: +44 (0) 121 371 5858;
e-mail: Richard.Borrows@uhb.nhs.uk

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Summary

Physical fatigue is debilitating and common among kidney transplant recipients (KTRs). This study investigated the mechanistic aetiology of physical fatigue in this setting through examinations of muscle mass, muscular and cardiovascular function, and perceived exertion. The incidence of physical fatigue, its association with quality of life (QoL), and the predictors of perceived exertion, were evaluated. This single-centre observational cross-sectional study enrolled 55 KTRs. Muscle mass was quantified using dual-energy x-ray absorptiometry. Muscular function was assessed by jumping mechanography. Cardiovascular function (maximal oxygen consumption and oxygen pulse) was estimated during submaximal exercise testing, with perceived exertion determined using age-adjusted Borg scale-ratings. Physical fatigue was measured using Multi-Dimensional Fatigue Inventory-20. QoL was assessed using Medical Outcomes Study Short Form-36. Demographic, clinical, nutritional, psychosocial and behavioural predictors of perceived exertion were assessed. Of clinical importance, increased perceived exertion was the only independent predictor of physical fatigue ($P = 0.001$), with no association found between physical fatigue and muscular or cardiovascular parameters. Physical fatigue occurred in 22% of KTRs, and negatively impacted on QoL ($P < 0.001$). Predictors of heightened perception included anxiety ($P < 0.05$) and mental fatigue ($P < 0.05$). Perception is a key determinant of physical fatigue in KTRs, paving the way for future interventions.

Introduction

Fatigue is the subjective sensation of profound and persistent tiredness, weakness, and lack of energy [1,2]. It is a complex and multi-dimensional phenomenon involving physical, cognitive and emotional components that interfere with individuals' abilities to function normally [2,3]. Fatigue is a prevalent patient-reported outcome among kidney transplant recipients (KTRs), occurring in up to 59% of these patients [3–5] and substantially impacting upon quality of life (QoL) [4,5]. Yet it is often medically unexplained, clinically under-recognized, and usually untreated [4].

One of the most frequently used instruments for fatigue assessment, namely Multi-Dimensional Fatigue Inventory-20 (MFI-20), measures physical, behavioural, emotional

and cognitive components contributing to the overall assessment of fatigue. Although KTRs displayed high scores in all aspects of fatigue [4], physical fatigue, found in 38% of KTRs [4], represents the dominant component outweighing behavioural, emotional and cognitive aspects [4], and impacts on all domains of QoL [4].

Conceptually, physical fatigue has traditionally been considered as a consequence of strenuous physical activity. Accordingly, excessive physical fatigue may be ascribed to either "cardiovascular", "muscular" or "perceptual" aetiologies. The cardiovascular model refers to insufficient cardiovascular oxygen or nutrient delivery to the muscular system, limiting oxidative phosphorylation and glycolysis, both essential mechanisms for muscle contraction [6]. Correspondingly, "cardiovascular" fatigue results in decreased ability of muscle to generate and maintain force, contributing to physical fatigue. The "muscular" model denotes insufficient muscle mass or reduced muscular function, leading to failure of muscle force generation [6–8], and/or inability to maintain force or power output [9], resulting in physical fatigue. The "perceptual" theory represents increased perception of effort, characterized by loss of motivation and reluctance to perform physical tasks when perception of effort reaches a certain level. In fatigue with perceptual origin, individuals experience heightened responses to a combination of feed forward signals from the motor centres and afferent feedback from the working body [6,10,11], resulting in depressed motivation with increasing exercise intensity and/or duration. The extent of inhibition varies, individuals with heightened perceived exertion experiencing a greater sense of effort for a given workload, expressed as physical fatigue. Of interest, it is recognized that mental fatigue, characterized by inability to focus and maintain cognitive attention, is a crucial determinant of physical limits in healthy individuals [12–14], by heightening the perception of exertion [12,13].

The cardinal mechanisms underlying physical fatigue in KTRs remain unexplored. The primary objectives of this study were to systematically examine the aetiology of physical fatigue in KTRs, by measuring factors which may be mechanistically linked to symptoms of physical fatigue. These include quantification of muscle mass, assessment of muscular and cardiovascular function, and evaluation of perceived exertion during a standardized exercise protocol. In addition, the incidence of physical fatigue, and its impact on QoL in clinically stable KTRs, were examined. The key findings were that physical fatigue affected 22% of clinically stable KTRs, adversely impacted on QoL, and was unrelated to cardiovascular or muscular factors. Rather, heightened perception of fatigue during exercise was closely related to physical fatigue. These findings led to further investigation to examine the role of mental fatigue, and other plausible predictors of heightened perception.

Subjects and methods

Participants and study design

Prevalent KTRs were recruited from the renal transplant outpatient clinic at Queen Elizabeth Hospital Birmingham UK, between August 2011 and August 2013. Inclusion and exclusion criteria are detailed in Table 1. Of 67 KTRs approached, 12 did not participate mainly because of work commitment. Age- and gender- matched healthy subjects (control group) were recruited over the same time period, from Queen Elizabeth Hospital Birmingham UK through recruitment posters, and from University of Birmingham UK by email invitations to all students and staff members. Of 45 volunteers, four were excluded because of the presence of known chronic illnesses and the use of regular medications.

The study was approved by the local research ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

Protocol overview

KTRs and controls attended the research visit in the morning following an overnight rest and a light breakfast (260 kcal; 12 g protein). Upon arrival, the testing procedures including the use of questionnaires, tools and equipment were explained.

The order of tests was standardized. First, blood sampling was undertaken. Self-completion of questionnaires, including MFI-20, Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), and Medical Outcomes Study Short-Form 36 (SF-36) followed. Then, Dual-Energy X-Ray Absorptiometry (DEXA) scanning and jumping mechanography were undertaken.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
• KTRs beyond 1 year post-transplantation
• Stable graft function (<10% increase in serum creatinine over the preceding 6 months)
Exclusion criteria
• Inability to provide written informed consent
• Episodes of acute rejection within the last 6 months
• Evidence of sepsis in the last 6 weeks
• Known active malignancy or chronic infection
• History of thyroid disease or adrenal insufficiency
• Evidence of unstable angina (occurring at rest, severe and of new onset, or crescendo pattern)
• Evidence of acute coronary syndrome in the last 6 months
• Moderate or severe aortic stenosis (mean transvalvular gradient of >25 mmHg or valve area of <1.5 cm^2 on echocardiogram)
• Immobility
• Pregnancy

Finally, participants rested for 1-h prior to performing an incremental submaximal exercise test, which included a measure of exertion using the Borg Rating of Perceived Exertion (RPE) scale.

MFI-20 and definition of physical fatigue

Severity of physical fatigue was assessed subjectively using the MFI-20, a 20-item self-report questionnaire measuring fatigue in five dimensions, with four items measuring physical fatigue using a 5-point Likert scale. Scores for physical fatigue ranged from 4-20, with higher scores indicating greater fatigue. See Appendix S1.

The incidence of physical fatigue was determined using the previously established definition of physical fatigue, defined as ≥95th percentile for the general population as reported by Lin *et al.* [4,15].

Dual-energy X-ray absorptiometry

DEXA provided measures of whole-body lean tissue mass (LTM), lower limb lean tissue mass (LLTM), and fat mass (FM) [16,17]. Both LTM and LLTM were normalized to height squared (Ht^2) accounting for differences in body size. See Appendix S1.

Jumping mechanography

The Leonardo Mechanography Ground Reaction Force Platform (Novotec Medical, Germany) was used to assess lower limb muscle power, an indication of muscular function. Participants performed a two-legged counter movement jump (CMJ) on the platform. Peak power of the vertical movement was computed by the system as the product of force and velocity [18–22], then normalized to total body mass (BM). Jumping mechanography predominately investigates kinetic factors of lower limb muscle function [23,24], peak power was also adjusted to LLTM. See Appendix S1.

Incremental submaximal exercise test

Cardiovascular function, represented by maximal oxygen consumption (VO_2max) and oxygen pulse (O_2 pulse), were measured by performing a submaximal incremental exercise test on an electrically braked cycle ergometer (Lode Corival, Cranlea, UK).

The exercise protocol was preceded and followed by 2-min warm-up and cool-down periods at 10 watts (W). The test started at 25W, with work rate increasing by 25W at 3-min intervals until voluntary exhaustion or the end of 3-min at 75W. Participants were encouraged verbally to maintain cadence ≥65 revolutions per minute.

Expired air volume and composition were collected continuously and analysed every 30 s using the MOXUS Modular Metabolic System (AEI Technologies, Pittsburgh, Pennsylvania, USA), providing oxygen consumption (VO_2). See Appendix S1. Heart rate (HR) was monitored continuously and recorded every 30 s (Polar Vantage NV, Kempele, Finland).

The VO_2 and HR measurements were averaged over the final minute of each 3-min workloads (25W, 50W and 75W). Consequently, VO_2max was estimated by linear regression of VO_2 as a function of HR, and extrapolating VO_2 to age-predicted maximum HR: *Age-predicted maximum HR = 205.8–(0.685 × Age)* [25–27]. Estimated VO_2max correlates highly with measured VO_2max when calculated with this approach [28]. An example of the linear regression is shown in Fig. 1a; the mean r^2 for the linear regression in the studied cohort was 0.97 ± 0.04.

O_2 pulse, oxygen consumed per heartbeat, was calculated as the gradient of the linear regression of VO_2 versus HR [29]. An example is shown in Fig. 1b; the mean r^2 for the cohort was 0.97 ± 0.05. O_2 pulse was expressed as absolute volume and adjusted for BM. To account for the effect of body size on O_2 pulse during exercise, O_2 pulse was also adjusted to LTM.

Perception of exertion

Perception of exertion was evaluated using the 15-point Borg RPE Scale [28]. This is a self-reported measure that evaluates the subjective perception of exertion on a scale of 6-20, with 6 representing "no exertion at all", and

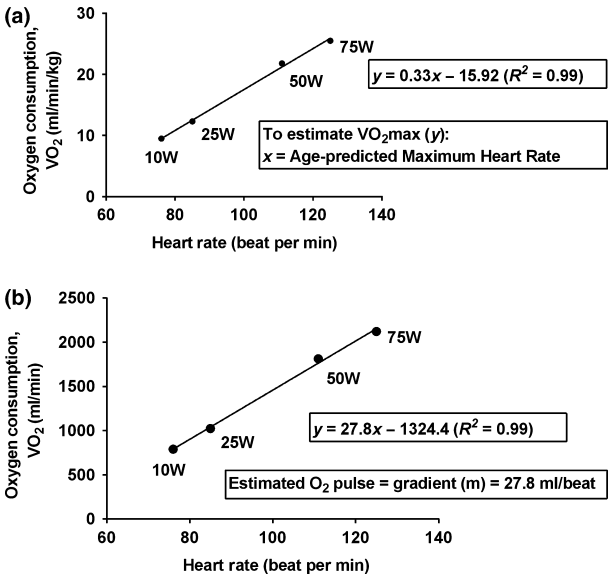

Figure 1 (a) An example of linear regression for estimation of maximal oxygen consumption (VO_2max). (b) An example of linear regression for estimation of oxygen pulse (O_2 Pulse).

20 denoting "maximal exertion". The RPE Scale was administered using standardized instructions provided by Borg [30]. Participants were familiarized with the scale prior to exercise testing. Although subjects received strong concurrent verbal encouragement throughout the exercise protocol, memory anchoring was not used. The RPE scale was displayed in sight of the participant during the entire exercise. In the last 5 s of each minute of the exercise, participants reported an instantaneous RPE by pointing at the scale.

To account for inter-individual differences in predicted maximum HR because of variations in age, a Rating of Perceived Exertion "Index" (RPE_{index}) was adopted for both within-group and between-group comparisons. To derive RPE_{index}, the *actual RPE* at the end of the exercise protocol (or volitional fatigue) was compared to the *expected RPE* based on the *subject's HR at that time* as a fraction of *estimated age-predicted maximum HR* and *assuming that RPE would be 20 at maximum HR*. RPE_{index} is therefore independent of age and absolute work rate, and hence a true reflection of the subject's sense of effort *per se*. Derivation is summarized as follows:

$$\begin{aligned} RPE_{index} = {} & (\text{Actual RPE}/\text{Expected RPE of 20}) \\ & \times (\text{Estimated Age} - \text{predicted Maximum HR}/ \\ & \text{Actual HR at exhaustion or end of exercise}) \end{aligned}$$

As such, a RPE_{index} of 1.0 is considered "normal", with values above this representing heightened perception of effort during this exercise protocol, and *vice versa*.

Quality of life assessment

SF-36 was used to assess QoL, consisting of 36 questions grouped into eight subscales corresponding to different life domains. It generates a total score for QoL, as well as physical- and mental-health scores. Within the SF-36, there is an "energy and vitality" subscale that measures fatigue [31]. Because of its confounding effect, correlations with physical fatigue were analysed prior to and following exclusion of this subscale. See Appendix S1.

Clinical, demographic, psychosocial and behavioural data collection

Blood sampling was undertaken from both KTRs and control group for analysis of high-sensitivity C-Reactive Protein (hsCRP), haemoglobin (Hb) and creatinine-derived estimated Glomerular Filtration Rate (eGFR) using the four-variable modification of diet in renal disease equation [32].

For both KTRs and control group, the following data were enquired by questionnaire: age, gender, marital status, ethnicity, smoking status (never smoked, current smoker, ex-smoker), alcohol intake (units per week), symptoms of anxiety and depression assessed using HADS, and sleep quality evaluated using PSQI. See Appendix S1.

For KTRs, the following data were collected from patient's medical records: time post-transplantation, co-morbidity assessed as Index of Co-Existing Disease (ICED) [33], presence of diabetes, either pretransplantation (pre-DM) or New Onset Diabetes After Transplantation (NODAT), prior acute rejection episodes, beta-adrenergic blocker and immunosuppressive medication usage.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 21 (Chicago, IL, USA). Regression diagnostics were performed. Results were presented as mean ± SD for normally distributed data, or median (interquartile range; IQR) for non-normal data. Chi-square or Fisher's exact tests were used to compare differences between groups on categorical variables. Mann–Whitney *U* test was used to compare differences between groups on ordinal variable. Independent-sample *t*-test was used to compare continuous data between groups.

Linear regression analysis was used to determine the association between predictor variable and the continuously-distributed outcome variable. There were two outcome variables in this study, physical fatigue and RPE_{index}, and both variables were tested for normality prior to regression analyses. The analyses were performed in three stages. Initially, the effect of each variable was examined in a series of univariate regression analyses. Then, interaction analyses moderated by the effect of gender, age and eGFR for each of the univariate relationships were performed. Subsequently, the joint effect of variables demonstrating some evidence of association in univariate analyses ($P < 0.20$) was examined in a multivariate regression analysis, using a fully adjusted multivariate model. A type I error rate $\leq 5\%$ ($p \leq 0.05$) was considered significant in the model. Specifically, the associations between each of the cardiovascular parameter and physical fatigue were adjusted for usage of beta-blockers.

Results

Population characteristics for the cohorts of KTRs and controls are shown in Table 2. Results for physical fatigue score, measurements of muscle mass and function, VO_2max, O_2 pulse and RPE_{index} for both cohorts are indicated in Table 3. The comparisons of these parameters between KTRs and control group are also shown in Table 3.

Table 2. Population characteristics for kidney transplant recipients (KTRs) and healthy subjects (control group).

	KTRs	Control group	*P*-value
Demographic parameters			
Sample size	*n* = 55	*n* = 41	n/a
Gender (%)	Male = 57 Female = 43	Male = 56 Female = 44	1.00‡
Mean age (years)*	46 ± 14	48 ± 12	0.94§
Marital status (%)	Single = 22 Married = 67 Divorced/Widowed = 11	Single = 20 Married = 68 Divorced/Widowed = 12	0.95¶
Ethnicity (%)	Caucasian = 80 Asian = 13 Afro-Caribbean = 5 Others = 2	Caucasian = 82 Asian = 12 Afro-Caribbean = 6 Others = 0	1.00‡,**
Median time post-transplantation (years)†	2 (1–7)	n/a	n/a
Co-morbidity and clinical parameters			
Median ICED†	2 (2–2)	n/a	n/a
Presence of diabetes (%)	Nondiabetic = 73 NODAT = 14 Pre-DM = 13	Nondiabetic = 100 NODAT = n/a Pre-DM = n/a	n/a n/a n/a
Previous episodes of acute rejection (%)	7	n/a	n/a
Use of beta-adrenergic blocker (%)	4	0	n/a
Immunosuppressive medication usage			
Calcineurin inhibitor (%)	93	n/a	n/a
Adjunctive antiproliferative agent (%)	87	n/a	n/a
Prednisolone (%)	86	n/a	n/a
Dosage of immunosuppressive medications			
Mean dose of tacrolimus (mg/day)*	5.8 ± 3.2	n/a	n/a
Mean dose of cyclosporine (mg/day)*	184 ± 47	n/a	n/a
Mean dose of mycophenolate mofetil (mg/day)*	1147 ± 456	n/a	n/a
Mean dose of azathioprine (mg/day)*	85 ± 36	n/a	n/a
Median dose of prednisolone (mg/day)†	5.3 (5.0–5.0)	n/a	n/a
Psychosocial & behavioural parameters			
Smoking status (%)	Nonsmoker = 60 Current smoker = 11 Ex-smoker = 29	Nonsmoker = 62 Current smoker = 8 Ex-smoker = 30	0.83¶
Median alcohol intake (units/week)†	2 (0–3)	3 (1–4)	0.32§
Mean anxiety score (HADS score)*	8 ± 5	4 ± 3	0.002††
Median depression score (HADS score)†	4 (1–6)	2 (1–3)	0.004††
Mean sleep quality score (PSQI global score)*	6 ± 3	4 ± 3	0.001††
Biochemical profile			
Median hsCRP (mg/l)†	1.67 (0.61–3.96)	0.92 (0.49–2.14)	0.01§
Mean Hb (g/dl)*	12.6 ± 1.5	14.0 ± 1.4	0.17§
Mean eGFR (ml/min)*	49.4 ± 12.9	82.2 ± 11.7	<0.001§

KTRs, kidney transplant recipients; ICED, index of co-existing disease; NODAT, new onset diabetes after transplantation; Pre-DM, pre-existing diabetes mellitus; HADS, hospital anxiety and depression scale; PSQI, Pittsburgh sleep quality index; hsCRP, high-sensitivity c-reactive protein; Hb, haemoglobin; eGFR, estimated glomerular filtration rate.

*Normally distributed data, results expressed as mean ± standard deviation (SD).

†Non-normally distributed data, results expressed as median (interquartile range, IQR).

‡Fisher's exact test was used to test statistical differences between 2 groups on categorical variables.

§Independent sample *t*-test was used to test statistical differences between 2 groups on the continuous variable.

¶Chi-square test was used to test statistical differences between 2 groups on the categorical variables.

**For the purpose of statistical analysis using Fisher's exact test, "Asian", "Afro-Caribbean" and "Others" were grouped as "Non-Caucasian".

††Mann–Whitney *U* test was used to test statistical differences between 2 groups on the ordinal variable.

Table 3. Measurements of physical and mental fatigue, quality of life, and potential predictors of physical fatigue in kidney transplant recipients (KTRs) and healthy subjects (Control group).

	KTRs	Control group	*P*-value
Physical fatigue			
Mean MFI-20 score†	10 ± 4	6 ± 3	<0.001‡
MFI-20 score ≥95th percentile for general population* (%)	22	3	0.006‡
Mental fatigue			
Mean MFI-20 score†	10 ± 5	7 ± 3	0.78‡
MFI-20 score ≥95th percentile for general population* (%)	20	5	0.18‡
Quality of life			
Mean total score†	77 ± 18	88 ± 10	0.01‡
Mean physical health summary score†	73 ± 20	85 ± 11	<0.001‡
Mean mental health summary score†	77 ± 18	87 ± 9	0.03‡

	KTRs			Control Group			*P*-value		
	All	Male	Female	All	Male	Female	All	Male	Female
Body composition (DEXA measurements)									
Mean LTM (kg)†	50.7 ± 11.5	58.0 ± 9.6	41.2 ± 4.9	52.3 ± 9.7	57.9 ± 7.4	44.8 ± 7.0	0.11§	0.31§	0.11§
Mean LTM adjusted to Ht^2 (kg/m^2)†	17.5 ± 2.5	18.7 ± 2.4	15.8 ± 1.6	17.8 ± 2.3	18.6 ± 1.7	16.7 ± 2.6	0.63§	0.81§	0.18§
Mean LLTM (kg)†	16.0 ± 3.7	18.1 ± 3.1	13.4 ± 2.4	17.0 ± 3.1	18.8 ± 2.6	14.4 ± 3.0	0.21§	0.78§	0.19§
Mean LLTM adjusted to Ht^2 (kg/m^2)†	5.5 ± 0.9	5.8 ± 0.8	5.0 ± 0.8	5.7 ± 0.9	6.1 ± 0.7	5.4 ± 1.1	0.22§	0.22§	0.21§
Mean FM (kg)†	26.1 ± 2.4	25.9 ± 2.3	26.1 ± 2.6	24.0 ± 2.1	22.9 ± 2.1	24.9 ± 2.2	0.26§	0.04§	0.67§
Jumping mechanography									
Mean muscle power from CMJ (W)†	2641 ± 756	3008 ± 727	2171 ± 493	2962 ± 727	3567 ± 745	2397 ± 523	0.12§	0.06§	0.31§
Mean muscle power per BM from CMJ (W/kg)†	35 ± 7	37 ± 8	32 ± 6	40 ± 7	47 ± 6	36 ± 7	0.10§	0.03§	0.25§
Mean muscle power per LLTM from CMJ (W/kg)†	169 ± 31	172 ± 33	166 ± 29	170 ± 30	177 ± 25	160 ± 30	0.45§	0.42§	0.41§
Incremental submaximal exercise test									
Mean VO_2max (ml/min/kg)†	27.7 ± 10.4	31.1 ± 10.7	22.4 ± 5.5	30.2 ± 8.1	35.0 ± 8.2	27.2 ± 6.7	0.13§	0.15§	0.02§
Mean O_2 Pulse (ml/beat)†	16.8 ± 5.8	21.6 ± 7.4	12.0 ± 4.2	20.1 ± 5.4	24.5 ± 5.5	17.2 ± 5.5	0.18§	0.26§	0.03§
Mean O_2 Pulse (ml/beat/kg BM)†	0.22 ± 0.07	0.26 ± 0.08	0.18 ± 0.06	0.26 ± 0.07	0.30 ± 0.06	0.24 ± 0.07	0.20§	0.21§	0.04§
Mean O_2 Pulse (ml/beat/kg LTM)†	0.35 ± 0.14	0.38 ± 0.13	0.30 ± 0.14	0.40 ± 0.08	0.42 ± 0.07	0.38 ± 0.09	0.22§	0.29§	<0.001§
Borg scale									
Mean RPE_{index}†	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.001§	0.001§	0.002§

MFI-20, multi-dimensional fatigue inventory-20; DEXA, dual energy x-ray absorptiometry; LTM, lean tissue mass; Ht^2, height squared; LLTM, lower limb lean tissue mass; FM, fat mass; CMJ, single two-legged counter movement jump; BM, total body mass; VO_2max, estimated maximal oxygen consumption; O_2 pulse, oxygen pulse; RPE_{index}, rating of perceived exertion index.

*Established definition of physical fatigue: ≥95^{th} percentile for general population reported by Lin *et al.* [4,15].

†Normally distributed data, results expressed as mean ± standard deviation (SD).

‡Mann–Whitney *U* test was used to test statistical differences between two groups on the ordinal variable.

§Independent sample *t*-test was used to test statistical differences between two groups on the continuous variable.

Muscular mass and function

Table 3 shows that LTM adjusted to Ht^2 and LLTM adjusted to Ht^2 did not differ significantly between KTRs and controls in either males or females.

Similarly, Table 3 indicates that jumping power derived from CMJ per kg LLTM did not differ significantly between KTRs and controls in either males or females. However, while jumping power from CMJ per kg BM did not differ significantly between female KTRs and female controls, it is

significantly lower in male KTRs compared to their control counterparts.

Importantly, in the analysis of KTRs, no correlation was found between physical fatigue and LTM adjusted to Ht^2 ($r = 0.09$, $P = 0.75$), LLTM adjusted to Ht^2 ($r = 0.05$, $P = 0.48$), muscular power from CMJ ($r = 0.18$, $P = 0.33$), or CMJ adjusted to BM ($r = 0.19$, $P = 0.31$), or CMJ adjusted to LLTM ($r = 0.24$, $P = 0.28$).

Cardiovascular function

Table 3 indicates that VO_2max, absolute O_2 pulse, O_2 pulse adjusted to BM, and O_2 pulse adjusted to LTM were significantly lower in female KTRs compared to female controls. No differences between male KTRs and controls were seen.

Of note, in the analyses relating to KTRs, no significant correlations were seen between physical fatigue and VO_2max ($r = 0.23$, $P = 0.09$), absolute O_2 pulse ($r = 0.17$, $P = 0.21$), O_2 pulse adjusted for BM ($r = 0.21$, $P = 0.20$), or O_2 pulse adjusted for LTM ($r = 0.17$, $P = 0.23$).

Perceived exertion

Figure 2 shows the overall distribution of RPE_{index} in KTRs and the control group. RPE_{index} was significantly higher in KTRs (1.0 ± 0.3) compared to controls (0.8 ± 0.2) ($P = 0.001$). Specifically, as shown in Table 3, RPE_{index} was significantly higher in both male (0.9 ± 0.3) and female (1.0 ± 0.2) KTRs compared to male (0.7 ± 0.2) and female (0.8 ± 0.2) controls, respectively.

Notably, in the regression analysis pertaining to KTRs, and in contrast to the lack of association between physical fatigue and either cardiovascular or muscular parameters, RPE_{index} demonstrated a significant, graded, and positive correlation with physical fatigue ($r = 0.42$, $P = 0.001$, Fig. 3).

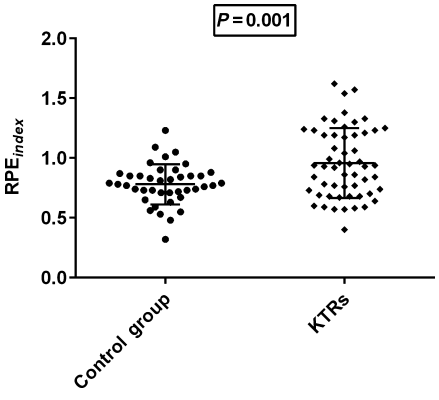

Figure 2 Comparison of rating of perceived exertion index (RPE_{index}) between healthy subjects (control group) and kidney transplant recipients (KTRs).

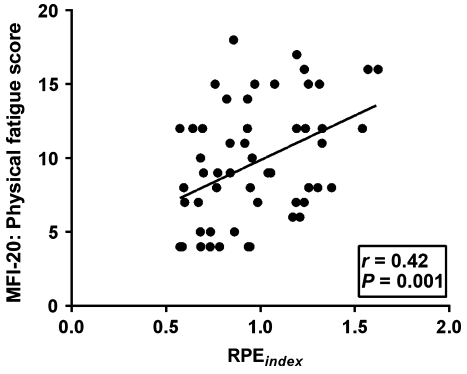

Figure 3 Association between physical fatigue and rating of perceived exertion index (RPE_{index}) in kidney transplant recipients (KTRs).

Predictors of physical fatigue in kidney transplant recipients

Physical fatigue scores were normally distributed and analysed on the original scale of measurement. Table 4 shows the associations between physical fatigue and measures of muscle mass and function, VO_2max, O_2 pulse and RPE_{index} in KTRs. On univariate analysis, the only significant predictor of increasing physical fatigue in KTRs was increased RPE_{index} ($\beta = 5.7$; 95% Confidence Interval [CI] = 2.2, 9.2; $r = 0.42$; $P = 0.001$, Fig. 3). No significant associations were seen between physical fatigue and measures of muscle mass and function. A trend towards an association between physical fatigue and VO_2max was evident on univariate analysis ($\beta = -0.1$; 95% CI = −0.2, 0.0; $r = 0.23$; $P = 0.09$), Fig. 4.

With RPE_{index} and VO_2max analysed in the fully adjusted multivariate model, VO_2max no longer retained significance ($\beta = -0.1$; 95% CI = −0.2, 0.1; $P = 0.43$). In this model, RPE_{index} remained the single independent predictor of physical fatigue ($\beta = 5.4$; 95% CI = 1.6, 9.3; $P = 0.001$). Of note, no significant age-, gender- and eGFR-interactions were found between physical fatigue and any predictor variables ($P > 0.05$ for all associations), see Appendix S2, Table 1.

Incidence of physical fatigue; and correlation with quality of life in kidney transplant recipients

As shown in Table 3, the mean score for physical fatigue in KTRs was 10 ± 4, higher than that reported by the control group at 6 ± 3 ($P < 0.001$; Fig. 5). Based on the established definition of physical fatigue (≥95th percentile for general population) [4,15], the incidence of physical fatigue in KTRs was 22%. Coincidentally, when the incidence of physical fatigue was categorized using ≥95th percentile for the control group, comparable incidence (22%) was identified.

Table 4. Predictors for mechanistic aetiology of physical fatigue in kidney transplant recipients (KTRs).

	Univariate Analysis		Multivariate analysis*	
	Beta Coefficient, β (95% CI)	*P*-value	Beta Coefficient, β (95% CI)	*P*-value
RPE_{index}	5.7 (2.2, 9.2)	0.001	5.4 (1.6, 9.3)	0.001
VO_2max (ml/min/kg)	−0.1 (−0.2, 0.0) †	0.09	−0.1 (−0.2, 0.1)	0.43
O_2 Pulse (ml/beat)	3.5 (−4.1, 11.2) †	0.21		
O_2 Pulse (ml/beat/kg BM)	2.5 (−2.7, 11.4) †	0.20		
O_2 Pulse (ml/beat/kg LTM)	4.7 (−3.1, 12.6) †	0.23		
LTM adjusted to Ht^2 (kg/m^2)	0.1 (−0.4, 0.5)	0.75		
LLTM adjusted to Ht^2 (kg/m^2)	−0.4 (−1.6, 0.8)	0.48		
CMJ, absolute power (W) ‡	−0.1 (−0.2, 0.1)	0.33		
CMJ, power per BM (W/kg) §	−0.1 (−0.2, 0.1)	0.31		
CMJ, power per LLTM (W/kg) §	−0.1 (−0.3, 0.1)	0.28		
R^2 value from the fully adjusted multivariate model			28%	

RPE_{index}, rating of perceived exertion index; VO_2max, estimated maximal oxygen consumption; O_2 pulse, oxygen pulse; BM, total body mass; LTM, lean tissue mass; Ht^2, height squared; LLTM, lower limb lean tissue mass; CMJ, single two-legged counter movement jump; CI, Confidence Interval.
*Results in the fully adjusted multivariate regression model were presented.
†Association adjusted for usage of beta-blockers.
‡Coefficients reported for a 100-unit increase in explanatory variable.
§Coefficients reported for a 10-unit increase in explanatory variable.

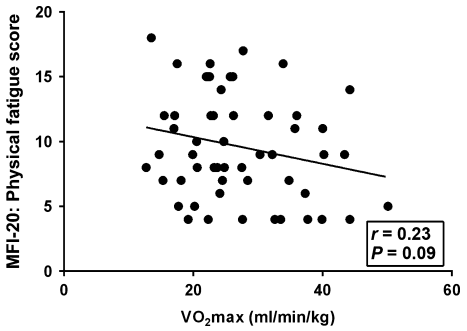

Figure 4 Association between physical fatigue and maximal oxygen consumption (VO_2max) in kidney transplant recipients (KTRs).

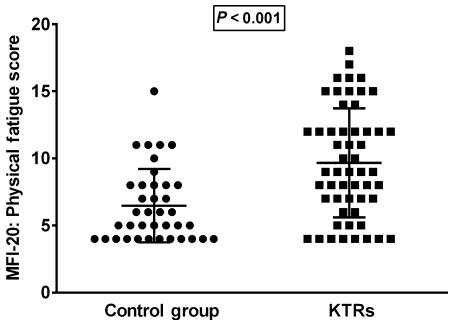

Figure 5 Comparison of physical fatigue scores between healthy subjects (control group) and kidney transplant recipients (KTRs).

Table 3 indicates that SF-36 total, physical and mental health summary scores for KTRs were significantly lower than the corresponding scores for the control group. In KTRs, physical fatigue correlated closely with SF-36 total score ($r = -0.68$; $P < 0.001$), SF-36 physical health summary score ($r = -0.74$; $P < 0.001$), and SF-36 mental health summary score ($r = -0.60$; $P < 0.001$), Fig. 6a. To exclude the confounding effect of the SF-36 "energy and vitality" subscale, which is a general measure of fatigue within SF-36 [31], results were reanalysed excluding this subscale, and the associations remained comparable after this exclusion [SF-36 total score $r = -0.65$ ($P < 0.001$), SF-36 physical health summary score $r = -0.71$ ($P < 0.001$), and SF-36 mental health summary score $r = -0.53$ ($P < 0.001$); Fig. 6b)].

Predictors of perceived exertion in kidney transplant recipients

Finally, in light of the association between RPE_{index} and physical fatigue in KTRs, and the previously described association between mental fatigue and perceived exertion in a nontransplant cohort [12], the impact of mental fatigue and other plausible predictors upon perceived exertion was examined in this cohort of KTRs.

Scores for RPE_{index} were normally distributed and analysed on the original scale of measurement. Measurements of the potential predictors of RPE_{index}, including demographic, clinical, nutritional, psychosocial and behavioural parameters are indicated in Tables 2 and 3. On univariate analysis, as shown in Table 5, mental fatigue, NODAT, absence of cyclosporine, increasing age, low alcohol intake, anxiety and depression were significantly associated with RPE_{index}. In the fully adjusted multivariate analysis, age and

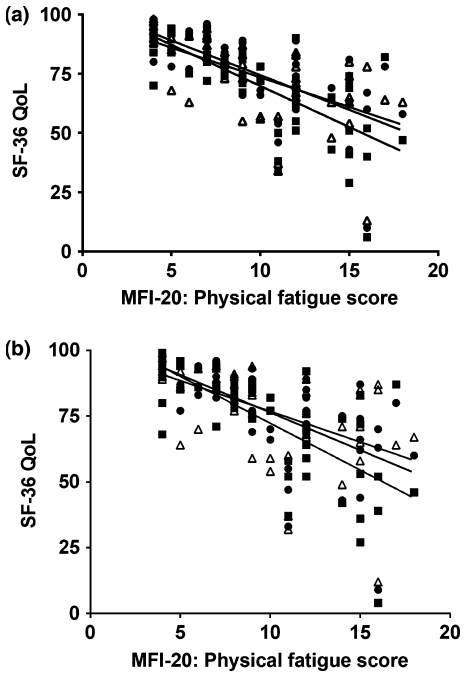

Figure 6 (a)Association between physical fatigue and quality of life (QoL) in kidney transplant recipients (KTRs) ~ All subscales. ● Physical fatigue versus SF-36 QoL (total score); $r = 0.68$, $P < 0.001$; ■ Physical fatigue versus SF-36 QoL (physical health summary score); $r = 0.74$, $P < 0.001$; △ Physical fatigue versus SF-36 QoL (mental health summary score); $r = 0.60$, $P < 0.001$ (b) Association between physical fatigue and quality of life (QoL) in kidney transplant recipients (KTRs) ~ excluding "Energy & Vitality" subscale. ● Physical fatigue versus SF-36 QoL (total score); $r = 0.65$, $P < 0.001$; ■ Physical fatigue versus SF-36 QoL (physical health summary score); $r = 0.71$, $P < 0.001$; △ Physical fatigue versus SF-36 QoL (mental health summary score); $r = 0.53$, $P < 0.001$.

depression did not retain significance, but the remaining variables remained significantly associated with RPE_{index} (Table 5).

Discussion

This is the first study to systematically investigate the potential aetiology of physical fatigue in KTRs, and reveals novel findings. Specifically, physical fatigue in KTRs seems unrelated to muscular and cardiovascular factors, but rather, it is driven by increased perception of exertion during exercise. In turn, mental fatigue is significantly associated with such heightened perception of effort. The findings of the current study also confirm physical fatigue as a common and disabling symptom among KTRs, negatively impacting on QoL [3–5]. Whilst novel to transplantation, these results resonate with recent findings emerged from other populations, whereby heightened perception limits exercise capacity in healthy trained individuals [34] and diabetic patients [35], and mental fatigue impairs physical performance in healthy subjects through increased perception of effort rather than limiting musculoenergetic or cardiovascular function [12,13]. In addition, observations in chronic fatigue syndrome (CFS) further support the findings from this study, corroborating that fatigue is not explained by deficits in the muscular and cardiovascular systems [36]. These results suggest that interventions directed towards the psychology rather than physiology of fatigue may be beneficial to KTRs with this important and debilitating symptom.

This is a single-centre pilot study of 55 patients, and validation is needed in larger cohorts. For ethical and safety reasons, the physiological testing was performed in a selected cohort of clinically stable KTRs, limiting the generalization of the results to the overall kidney transplant population. However, the focus of the current study was to specifically address physical fatigue in this context, enabling evaluation without the confounding effect of intercurrent or chronic illnesses. Thus, it is noteworthy that despite this targeted enrolment, and based on the established definition of physical fatigue (≥95th percentile for general population) [4,15], 22% of KTRs experienced significant physical fatigue. Indeed, the mean physical fatigue score in KTRs (10 ± 4) was higher than healthy subjects in the control group (6 ± 3), and comparable to "chronically unwell" patients (10 ± 4) reported previously by Lin *et al.* [15]. This, together with the adverse associations with all aspects of QoL, indicates the severity of the problem.

Varied disease processes, immunosuppression with steroid therapy, and lack of physical activity may result in muscle atrophy. In these circumstances, muscles work at a relatively high work-load even in everyday life, and hence fatigue rapidly. However, whole body LTM and LLTM in KTRs were comparable to healthy subjects in the control group, and there was no association between physical fatigue with either whole body LTM or LLTM in KTRs. In support of these results, muscle mass was comparable to previous literature in this field [37,38]. Certainly, muscle mass *per se* may not be the crucial factor, the ability of musculature to generate force and movement may be of greater importance. Interestingly, the results from the jumping mechanography studies showed that KTRs were mostly capable of generating muscular power similar to healthy subjects in the control group, apart from the observation that male KTRs displayed significantly lower muscular power adjusted to body weight compared to healthy subjects in the control group. Such discrepancy may be explained by significantly higher adiposity measured by DEXA among male KTRs compared to male controls. Nevertheless, there were no associations between any measure of muscular power and physical fatigue among KTRs.

VO_2max is the conventional measure of cardiovascular fitness, and its prognostic utility is well-established in

Table 5. Predictors of rating of perceived exertion index (RPE_{index}) in kidney transplant recipients (KTRs).

	Univariate analysis		Multivariate analysis*	
	Beta Coefficient, β (95% CI)	*P*-value	Beta Coefficient, β (95% CI)	*P*-value
Presence of diabetes				
Nondiabetic	0	0.02	0	0.04
NODAT	0.3 (0.0, 0.5)		0.2 (0.0, 0.5)	
Pre-DM	0.6 (−0.2, 1.4)		0.2 (−0.0, 0.5)	
Use of calcineurin inhibitor				
None	0	0.03	0	0.03
Cyclosporine	−0.3 (−0.5, −0.1)		−0.4 (−0.6, −0.2)	
Tacrolimus	−0.1 (−0.3, 0.2)		−0.0 (−0.3, 0.3)	
Mental fatigue (MFI-20 score) ‡	0.3 (0.1, 0.5)	0.04	0.5 (0.1, 0.9)	0.03
Anxiety (HADS score) ‡	0.5 (0.1, 0.8)	0.04	0.4 (0.1, 0.7)	0.04
Alcohol intake (units per week) ‡	−0.4 (−1.1, −0.0)	0.04	−0.6 (−1.1, −0.1)	0.03
Age (years) ‡	0.1 (0.0, 0.2)	0.04	0.1 (−0.1, 0.2)	0.21
Depression (HADS score) ‡	0.5 (0.0, 0.1)	0.05	0.1 (−0.2, 0.5)	0.37
Use of prednisolone				
No	0	0.10	0	
Yes	−0.4 (−0.9, 0.1)		−0.1 (−0.3, 0.1)	0.25
Co-morbidity (ICED score)	0.9 (−0.4, 2.2)	0.18	0.1 (−0.5, 0.6)	0.35
Previous episodes of acute rejection				
No	0	0.20		
Yes	−0.4 (−1.1, 0.2)			
Time post transplantation (years)	0.1 (−0.2, 0.4)	0.35		
Marital status				
Married	0	0.46		
Single	0.2 (−0.6, 0.2)			
Divorced/Widowed	−0.0 (−0.2, 0.1)			
Ethnicity†				
Caucasian	0	0.48		
Non-Caucasian‡	0.4 (−0.2, 3.8)			
Gender				
Female	0	0.51		
Male	0.1 (−0.2, 0.5)			
FM (kg) ‡	0.1 (−0.2, 0.3)	0.55		
Smoking status				
Never smoked	0	0.66		
Ex-smoker‡	0.5 (−1.6, 2.4)			
Current smoker	0.1 (−7.3, 7.6)			
Hb (g/dl) ‡	0.3 (−0.9, 1.5)	0.66		
PSQI (global score) ‡	0.1 (−0.5, 0.6)	0.77		
eGFR (ml/min) ‡	0.0 (−0.1, 0.2)	0.82		
hsCRP (mg/l) §	0.0 (−0.3, 0.4)	0.94		
Use of adjunctive antiproliferative agents				
None	0			
Mycophenolate mofetil‡	−0.2 (−4.3, 0.4)	0.98		
Azathioprine	0.0 (−0.3, 0.3)			
LTM (kg) ‡	0.00 (−0.2, 0.2)	0.99		
R^2 value from the fully adjusted multivariate model			38%	

NODAT, new onset diabetes after transplantation; Pre-DM, pre-existing diabetes mellitus; MFI-20, multi-dimensional fatigue inventory-20; HADS, hospital anxiety and depression scale; ICED, index of co-existing disease; FM, fat mass; Hb, haemoglobin; PSQI, Pittsburgh sleep quality index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; LTM, lean tissue mass; CI, Confidence Interval.

*Results in the fully adjusted multivariate regression model were presented.

†For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 80% "Caucasian" versus 20% "Non-Caucasian".

‡Coefficients reported for a 10-unit increase in explanatory variable.

§Variable analysed on the log scale (base 10).

research and clinical settings [39,40]. In this study, VO_2max was estimated by extrapolating oxygen uptake from the relationship with HR during a submaximal exercise test. This is a common approach [27], although there are two caveats. Firstly, estimation of maximum HR in relation to age can be unreliable [25,41]. Secondly, the conventional expression of body weight-adjusted VO_2max may be misleading because of inter-individuals' variability in body composition. Accordingly, fat mass may influence VO_2max measurement that has limited relevance to actual cardiovascular function. An alternative, but complimentary measure of O_2 pulse has recently emerged [39,40]. O_2 pulse is independent of body composition and maximum HR, and predominately determined by cardiac stroke volume and peripheral oxygen extraction during exercise, thereby potentially reflecting cardiovascular function more accurately [39,40,42]. Both male and female KTRs had numerically lower VO_2max and O_2 pulse measures compared to healthy subjects in the control group, albeit only of statistical significance in females. In support of these results, VO_2max data were comparable to findings from previous studies in this field [37,38,43,44]. Of note, neither VO_2max nor O_2 pulse were associated with physical fatigue in KTRs in the adjusted multivariate analysis. The difference in cardiovascular fitness between KTRs and healthy subjects is perhaps unsurprising, but identifying the underlying reasons for this was not the focus of the current study.

In contrast, it was RPE_{index} that independently and significantly correlated with physical fatigue in KTRs, consistent with a heightened perception of exertion. It should be noted that this derived index takes into account predicted maximal HR, and is therefore not a reflection of age, cardiovascular fitness and absolute work rate. The RPE_{index} represents an objective evaluation of perceived exertion during a protocolled exercise test. In the absence of evidence that cardiovascular or muscular mechanisms were associated with physical fatigue, the results of this study suggest that modifying the perception of fatigue may be the key to alleviate this symptom.

The mechanisms by which perception of effort influences physical performance has been proposed by Marcora and colleagues using the Brehm's theory of motivation [12]. In this theory, individuals opt to withdraw from a task when it is perceived to be too difficult, or the effort required exceeds the individuals' willingness to perform [45]. During the decision-making process, individuals are suspected to have lowered their level of task difficulty for withdrawal [46,47], and indeed, impaired physical performance is a common feature in KTRs [48,49].

In turn, KTRs displayed considerable mental fatigue, with MFI-20 scores of 10 ± 5, comparable to "chronically unwell" patients (11 ± 4) reported by Lin *et al.* [15]. Furthermore, mental fatigue was an independent predictor of increased perception of exertion. This novel finding in KTRs is highly reminiscent of that from Marcora *et al.* [12] in a nontransplant cohort, whereby experimentally induced mental fatigue decreases physical performance via increased perception of effort, without affecting conventional physiological variables such as stroke volume, oxygen uptake, blood pressure or lactate levels [12]. In addition, it has been shown that experimentally induced mental fatigue does not affect neuromuscular function [13], suggesting a failure of central motivation driving physical fatigue. Mental fatigue was measured by self-report questionnaire in this study, whereas mental fatigue was induced experimentally by a 90-min computer-based cognitive task in Marcora's study [12], hence it is unclear whether the two methodologies characterized equivalent effects. Yet the similarities between the studies are noteworthy, and it is highly plausible that increased perception of exertion results from mental fatigue among KTRs, contributing to symptoms of physical fatigue.

In this study, the mean anxiety score for KTRs on HADS was 8 ± 5, considered as mild anxiety [50]. Increased anxiety was independently associated with heightened perceived exertion. Depression also displayed a univariate association with increased perceived exertion. These observations were noted in previous studies of nontransplant cohorts [51,52], highlighting the relevance of the current findings. However, a caveat with the interpretation of the associations between self-reported data should be acknowledged, known as "common method variance" [53]. This includes symptoms of physical and mental fatigue, perceived exertion, anxiety and depression, whereby patients in negative mood perceive, remember, and report more physical and psychological symptoms, and report those symptoms to be more severe than patients with less negative mood [54]. Dissecting the differences between the self-reported symptoms of "psychological distress" requires detailed psychological evaluation, and such evaluation was beyond the scope of the current study. Nevertheless, the findings of the current study point towards psychological factors rather than physiological underperformance as the drivers of physical fatigue in KTRs. Future studies should focus on testing interventional strategies aiming to improve psychological factors. Exercise intervention, cognitive behavioural therapy (CBT) and centrally acting pharmacological therapy may be beneficial in this setting. Exercise-based interventions have shown promising results in relieving anxiety and depressive symptoms [55,56], and may indirectly improve perception of fatigue. Exercise therapy has also demonstrated efficacy in alleviating symptoms of fatigue in CFS [57]. A recent preclinical study showed that exercise training increases brain mitochondrial biogenesis, contributing to reductions in centrally mediated fatigue [58]. The exact mechanisms for these changes are unknown, but it is

possible that increased brain mitochondria plays an important role in reducing fatigue through their influence on cerebral energy status [58]. CBT *per se* or with exercise integration were found effective in treating symptoms of fatigue and mood in somatoform disorders, CFS, or fibromyalgia [59–61], and such approaches may be applicable in this setting. The use of centrally acting pharmacological therapy may also be considered. Selective serotonin reuptake inhibitors (SSRI) are used in patients with marked fatigue resulting from significant anxiety [62], and they reduce fatigue in depressed patients with multiple sclerosis through positive effects on mood [63].

The commonly studied clinical and demographic variables, including eGFR, Hb and hsCRP, showed no associations with perception of effort in KTRs. Other factors which were associated with heightened perceived exertion in KTRs included NODAT, absence of cyclosporine, and low alcohol intake. These correlations may be biologically plausible [64–69], although the possibility of type I statistical error should be acknowledged.

In conclusion, it is likely that improving physical fitness or function *per se* may not improve physical fatigue, and other strategies such as exercise interventions, cognitive behavioural therapy or centrally acting pharmacological therapies may be more appropriate. The findings of this study set the scene for future interventional research and therapeutic strategies.

Authorship

WC, DJ, JAB and RB: designed the research. WC, DJ, JAB, PGMcT, ACP and RB: wrote the manuscript. WC, JMcP, NC, OK, NI, SM, AMcC, LH and RB: conducted the research. WC, DJ, JAB, ACP and RB: analysed the data and performed the statistical analysis. WC and RB: had primary responsibility for the final content.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Subjects and Methods.

Appendix S2. Results.

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