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Cardiovascular, Muscular and Perceptual Contributions to Physical Fatigue in Prevalent Kidney Transplant Recipients

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Running Title

Physical Fatigue in Kidney Transplant Recipients

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Author Contributions

Winnie Chan, David Jones, Jos A Bosch, and Richard Borrows designed the research.

Winnie Chan, David Jones, Jos A Bosch, Philip G McTernan, Anna C Phillips, and Richard Borrows wrote the manuscript.

Winnie Chan, Jamie McPhee, Nicola Crabtree, Okdeep Kaur, Nicholas Inston, Sue Moore, Andrew McClean, Lorraine Harper, and Richard Borrows conducted the research.

Winnie Chan, David Jones, Jos A Bosch, Anna C Phillips, and Richard Borrows analysed the data and performed the statistical analysis.

Winnie Chan and Richard Borrows had primary responsibility for the final content.

Abbreviations

BM	Body Mass
CBT	Cognitive Behavioural Therapy
CFS	Chronic Fatigue Syndrome
CI	Confidence Interval
CMJ	Counter Movement Jump

DEXA	Dual-Energy X-Ray Absorptiometry
eGFR	Estimated Glomerular Filtration Rate
FM	Fat Mass
HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
hsCRP	High-Sensitivity C-Reactive Protein
Hb	Haemoglobin
Ht ²	Height Squared
ICED	Index of Co-Existing Disease
IQR	Interquartile Range
KTRs	Kidney Transplant Recipients
LLTM	Lower Limb Lean Tissue Mass
LTM	Lean Tissue Mass
MFI-20	Multi-Dimensional Fatigue Inventory-20
NODAT	New-Onset Diabetes After Transplantation
O ₂ pulse	Oxygen Pulse
Pre-DM	Presence of Diabetes Pre-Transplantation
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of Life
RPE	Rating of Perceived Exertion
RPE _{index}	Rating of Perceived Exertion Index
SD	Standard Deviation
SF-36	Medical Outcomes Study Short-Form 36
SSRI	Selective Serotonin Reuptake Inhibitors
VO ₂	Oxygen Consumption
VO ₂ max	Maximal Oxygen Consumption
W	Watts

Abstract

Background: 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.

Methods: 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.

Results: 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 ($p<0.05$).

Conclusion: 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-recognised, 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, characterised 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 recognised that mental fatigue, characterised 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 standardised 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 due to work commitment. Age- and gender- matched healthy subjects (control group) were

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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, 4 were excluded due to 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 (260kcal; 12g protein). Upon arrival, the testing procedures including the use of questionnaires, tools and equipment were explained.

The order of tests was standardised. First, blood sampling was undertaken. Self-completion of questionnaires, including Multi-Dimensional Fatigue Inventory-20 (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. Finally, participants rested for one-hour prior to performing an incremental submaximal exercise test, which included a measure of exertion using the Borg Rating of Perceived Exertion (RPE) scale.

Multi-Dimensional Fatigue Inventory-20 (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 5 dimensions, with 4 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 **Supporting Information, Subjects and Methods**.

The incidence of physical fatigue was determined using the previously established definition of physical fatigue, defined as $\geq 95^{\text{th}}$ 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 normalised to height squared (Ht^2) accounting for differences in body size. See **Supporting Information, Subjects and Methods**.

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 normalised 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 **Supporting Information, Subjects and Methods**.

Incremental Submaximal Exercise Test

Cardiovascular function, represented by maximal oxygen consumption ($VO_{2\text{max}}$) 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 two-minute warm-up and cool-down periods at 10 watts (W). The test started at 25W, with work rate increasing by 25W at three-minute intervals until voluntary exhaustion or the end of three-minute at 75W. Participants were encouraged verbally to maintain cadence ≥ 65 revolutions per minute. This article is protected by copyright. All rights reserved.

Expired air volume and composition were collected continuously and analysed every 30 seconds using the MOXUS Modular Metabolic System (AET Technologies, USA), providing oxygen consumption (VO_2). See **Supporting Information, Subjects and Methods**. Heart rate (HR) was monitored continuously and recorded every 30 seconds (Polar Vantage, Finland).

The VO_2 and HR measurements were averaged over the final minute of each three-minute workloads (25W, 50W and 75W). Consequently, $\text{VO}_{2\text{max}}$ 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 = $205.8 - (0.685 \times \text{Age})$* (25-27). Estimated $\text{VO}_{2\text{max}}$ correlates highly with measured $\text{VO}_{2\text{max}}$ when calculated with this approach (28). An example of the linear regression is shown in **Figure 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 **Figure 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 20 denoting “maximal exertion”. The RPE Scale was administered using standardised instructions provided by Borg (30). Participants were familiarised 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. This article is protected by copyright. All rights reserved.

In the last 5 seconds 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 due to 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 summarised as follows:

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

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 8 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). Due to its confounding effect, correlations with physical fatigue were analysed prior to and following exclusion of this subscale. See **Supporting Information, Subjects and Methods**.

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 4-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 **Supporting Information, Subjects and Methods**.

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 pre-transplantation (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). Regression diagnostics were performed. Results were presented as mean \pm 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**.

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 ($r=0.42$, $p=0.001$, **Figure 3**).

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 $\text{RPE}_{\text{index}}$ in KTRs. On univariate analysis, the only significant predictor of increasing physical fatigue in KTRs was increased $\text{RPE}_{\text{index}}$ ($\beta=5.7$; 95% Confidence Interval [CI]=2.2, 9.2; $r=0.42$; $p=0.001$, **Figure 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; $r=0.23$; $p=0.09$), **Figure 4**.

With $\text{RPE}_{\text{index}}$ 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, $\text{RPE}_{\text{index}}$ 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 **Supporting Information, Results, 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 ($p<0.001$; **Figure 5**). Based on the established definition of physical fatigue ($\geq 95^{\text{th}}$ percentile for general population) (4, 15), the incidence of physical fatigue in KTRs was 22%. Coincidentally, when the incidence of physical fatigue was categorised using $\geq 95^{\text{th}}$ percentile for the control group, comparable incidence (22%) was identified.

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 ($r=-0.60$; $p<0.001$), **Figure 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 $r=-0.53$ ($p<0.001$); **Figure 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 non-transplant 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 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 generalisation 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 ($\geq 95^{\text{th}}$ 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.

VO₂max is the conventional measure of cardiovascular fitness, and its prognostic utility is well-established in research and clinical settings (39, 40). In this study, VO₂max 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 2 caveats. Firstly, estimation of maximum HR in relation to age can be unreliable (25, 41). Secondly, the conventional expression of body weight-adjusted VO₂max may be misleading due to inter-individuals' variability in body composition. Accordingly, fat mass may influence VO₂max measurement that has limited relevance to actual cardiovascular function. An alternative, but complimentary measure of O₂ pulse has recently emerged (39, 40). O₂ pulse

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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 was 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 $\text{RPE}_{\text{index}}$ 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 $\text{RPE}_{\text{index}}$ 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).

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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). Further, 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 in a non-transplant cohort (12), 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-minute computer-based cognitive task in Marcora’s study (12), hence it is unclear whether the two methodologies characterised 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 non-transplant 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. This article is protected by copyright. All rights reserved.

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 pre-clinical 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.

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Table Legends

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|-----------------|---|
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Potential Predictors of Physical Fatigue in Kidney Transplant Recipients
(KTRs) and Healthy Subjects (Control Group)

Table 4. Predictors for Mechanistic Aetiology of Physical Fatigue in Kidney Transplant Recipients (KTRs)

Table 5. Predictors of Rating of Perceived Exertion Index (RPE_{index}) in Kidney Transplant Recipients (KTRs)

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 >25mmHg or valve area of <1.5cm ² on echocardiogram)
▪	Immobility
▪	Pregnancy

Table 2. Population Characteristics for Kidney Transplant Recipients (KTRs) and Healthy Subjects (Control Group)

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

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)

Physical fatigue	KTRs			Control Group			P-value		
† Mean MFI-20 score	10 ± 4			6 ± 3			<0.001 ^a		
MFI-20 score ≥95 th percentile for general population* (%)	22			3			0.006 ^a		
Mental fatigue	KTRs			Control Group			P-value		
† Mean MFI-20 score	10 ± 5			7 ± 3			0.78 ^a		
MFI-20 score ≥95 th percentile for general population* (%)	20			5			0.18 ^a		
Quality of Life	KTRs			Control Group			P-value		
† Mean total score	77 ± 18			88 ± 10			0.01 ^a		
† Mean physical health summary score	73 ± 20			85 ± 11			<0.001 ^a		
† Mean mental health summary score	77 ± 18			87 ± 9			0.03 ^a		
Body composition (DEXA measurements)	KTRs			Control Group			P-value		
	All	Male	Female	All	Male	Female	All	Male	Female
† 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 ^b	0.31 ^b	0.11 ^b
† 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 ^b	0.81 ^b	0.18 ^b
† 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 ^b	0.78 ^b	0.19 ^b
† 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 ^b	0.22 ^b	0.21 ^b
† 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 ^b	0.04 ^b	0.67 ^b
Jumping mechanography	KTRs			Control Group			P-value		
	All	Male	Female	All	Male	Female	All	Male	Female
† Mean muscle power from CMJ (W)	2641 ± 756	3008 ± 727	2171 ± 493	2962 ± 727	3567 ± 745	2397 ± 523	0.12 ^b	0.06 ^b	0.31 ^b
† Mean muscle power per BM from CMJ (W/kg)	35 ± 7	37 ± 8	32 ± 6	40 ± 7	47 ± 6	36 ± 7	0.10 ^b	0.03 ^b	0.25 ^b
† Mean muscle power per LLTM from CMJ (W/kg)	169 ± 31	172 ± 33	166 ± 29	170 ± 30	177 ± 25	160 ± 30	0.45 ^b	0.42 ^b	0.41 ^b
Incremental submaximal exercise test	KTRs			Control Group			P-value		
	All	Male	Female	All	Male	Female	All	Male	Female
† Mean VO ₂ max (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 ^b	0.15 ^b	0.02 ^b
† 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 ^b	0.26 ^b	0.03 ^b
† 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 ^b	0.21 ^b	0.04 ^b
† 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 ^b	0.29 ^b	<0.001 ^b

Borg scale	KTRs			Control Group			P-value		
	All	Male	Female	All	Male	Female	All	Male	Female
[†] 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 ^b	0.001 ^b	0.002 ^b

[†]Normally distributed data, results expressed as mean ± standard deviation (SD). ^{*}Established definition of physical fatigue: ≥95th percentile for general population reported by Lin et al (4, 15).
^aMann-Whitney U test was used to test statistical differences between 2 groups on the ordinal variable. ^bIndependent sample t-test was used to test statistical differences between 2 groups on the continuous variable.
Abbreviations: MFI-20=multi-dimensional fatigue inventory-20; DEXA=dual energy x-ray absorptiometry; LTM=lean tissue mass; Ht²=height squared; LLTM=lower limb lean tissue mass; FM=fat mass; CMJ=single two-legged counter movement jump; BM=total body mass; VO₂max=estimated maximal oxygen consumption; O₂ pulse =oxygen pulse; RPE_{index}=rating of perceived exertion index.

Table 4. Predictors for Mechanistic Aetiology of Physical Fatigue in Kidney Transplant Recipients (KTRs)

	Univariate Analysis		Multivariate analysis*	
	Beta Coefficient, β (95% CI**)	<i>p</i> -value	Beta Coefficient, β (95% CI**)	<i>p</i> -value
RPE _{index}	5.7 (2.2, 9.2)	0.001	5.4 (1.6, 9.3)	0.001
VO ₂ max (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		
R² value from the fully adjusted multivariate model			28%	

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

**CI = Confidence Interval.

***Association adjusted for usage of beta-blockers.

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

‡Coefficients reported for a 100-unit increase in explanatory variable.

Abbreviations: RPE_{index}=rating of perceived exertion index; VO₂max=estimated maximal oxygen consumption; O₂ pulse=oxygen pulse; BM=total body mass; LTM=lean tissue mass; Ht²=height squared; LLTM=lower limb lean tissue mass; CMJ=single two-legged counter movement jump.

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				
Non-diabetic	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	0.25
Yes	-0.4 (-0.9, 0.1)		-0.1 (-0.3, 0.1)	
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	0.98		
†Mycophenolate mofetil	-0.2 (-4.3, 0.4)			
Azathioprine	0.0 (-0.3, 0.3)			
†LTM (kg)	0.00 (-0.2, 0.2)	0.99		
R² value from the fully adjusted multivariate model			38%	

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

**CI = Confidence Interval.

***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).

Abbreviations: 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.

Figure Legends

- Figure 1a:** An Example of Linear Regression for Estimation of Maximal Oxygen Consumption ($VO_2\text{max}$)
- Figure 1b:** An Example of Linear Regression for Estimation of Oxygen Pulse (O_2 Pulse)
- 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)
- Figure 4:** Association between Physical Fatigue and Maximal Oxygen Consumption ($VO_2\text{max}$) in Kidney Transplant Recipients (KTRs)
- Figure 5:** Comparison of Physical Fatigue Scores between Healthy Subjects (Control Group) and Kidney Transplant Recipients (KTRs)
- Figure 6a:** Association between Physical Fatigue and Quality of Life (QoL) in Kidney Transplant Recipients (KTRs) ~ All Subscales
- Figure 6b:** Association between Physical Fatigue and Quality of Life (QoL) in Kidney Transplant Recipients (KTRs) ~ Excluding “Energy & Vitality” Subscale

Figure 1a: An Example of Linear Regression for Estimation of Maximal Oxygen Consumption (VO_2max)

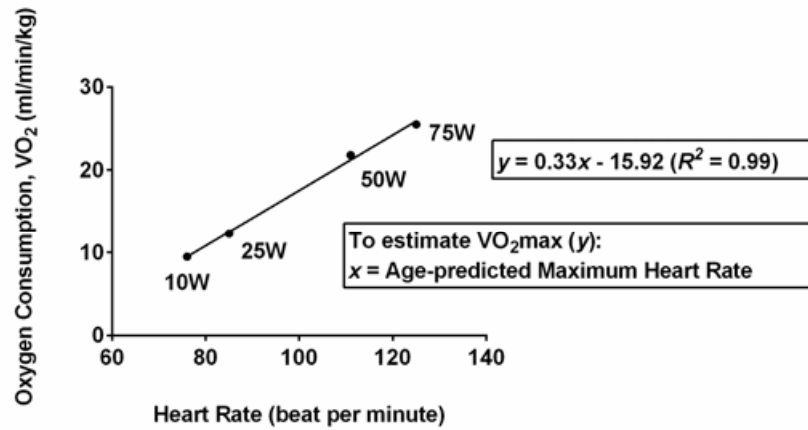


Figure 1b: An Example of Linear Regression for Estimation of Oxygen Pulse (O_2 Pulse)

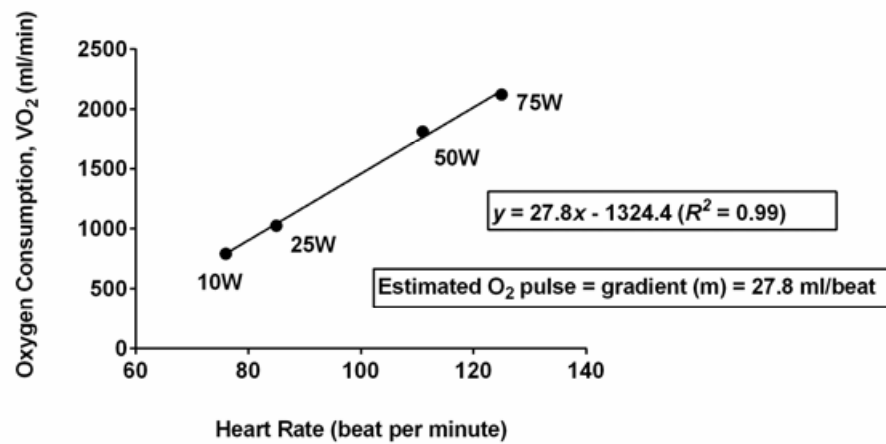


Figure 2: Comparison of Rating of Perceived Exertion Index (RPE_{Index}) between Healthy Subjects (Control Group) and Kidney Transplant Recipients (KTRs)

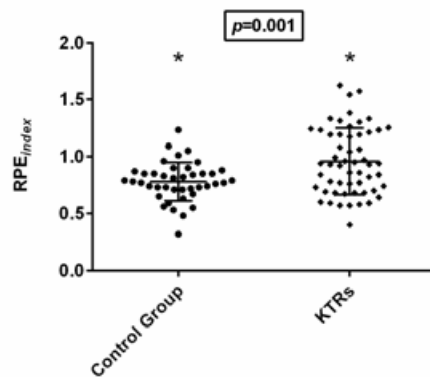


Figure 3: Association between Physical Fatigue and Rating of Perceived Exertion Index (RPE_{Index}) in Kidney Transplant Recipients (KTRs)

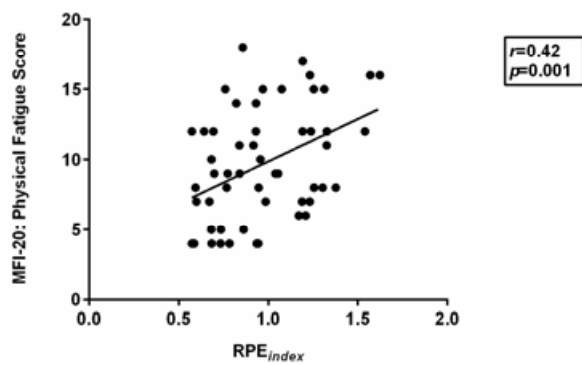


Figure 4: Association between Physical Fatigue and Maximal Oxygen Consumption (VO_2max) in Kidney Transplant Recipients (KTRs)

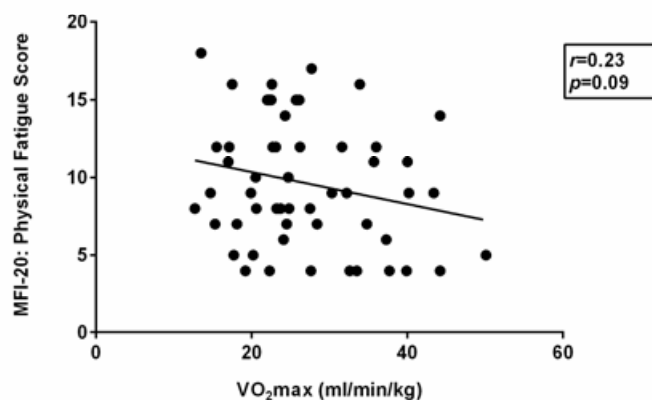


Figure 5: Comparison of Physical Fatigue Scores between Healthy Subjects (Control Group) and Kidney Transplant Recipients (KTRs)

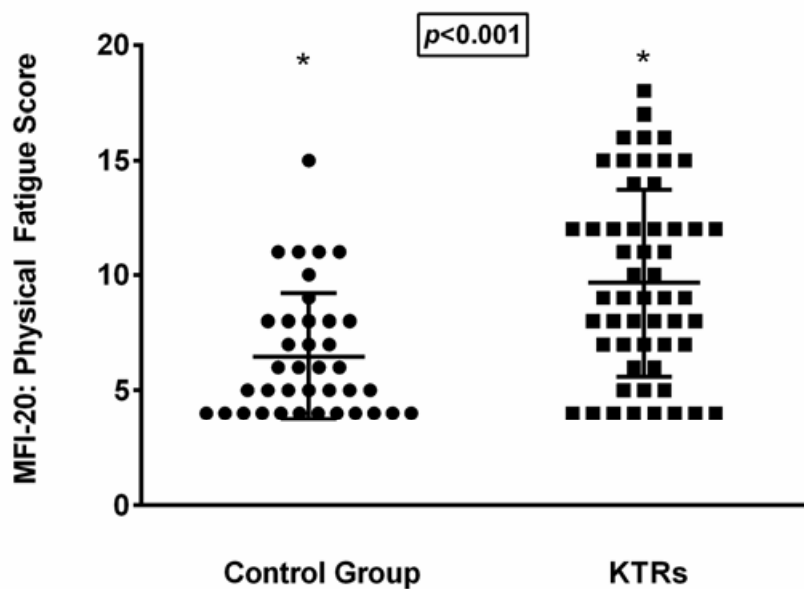


Figure 6a: Association between Physical Fatigue and Quality of Life (QoL) in Kidney Transplant Recipients (KTRs) ~ All Subscales

- ◆ Physical Fatigue vs SF-36 QoL (Total Score); $r=-0.68$, $p<0.001$
- Physical Fatigue vs SF-36 QoL (Physical Health Summary Score); $r=-0.74$, $p<0.001$
- △ Physical Fatigue vs SF-36 QoL (Mental Health Summary Score); $r=-0.60$, $p<0.001$

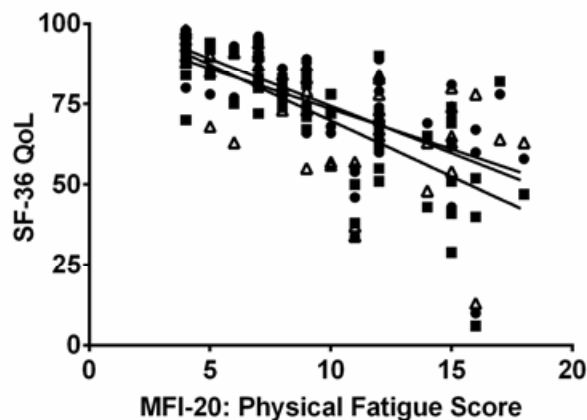


Figure 6b: Association between Physical Fatigue and Quality of Life (QoL) in Kidney Transplant Recipients (KTRs) ~ Excluding "Energy & Vitality" Subscale

- ◆ Physical Fatigue vs SF-36 QoL (Total Score); $r=-0.65$, $p<0.001$
- Physical Fatigue vs SF-36 QoL (Physical Health Summary Score); $r=-0.71$, $p<0.001$
- △ Physical Fatigue vs SF-36 QoL (Mental Health Summary Score); $r=-0.53$, $p<0.001$

