Peak aerobic capacity from incremental shuttle walk test in chronic kidney disease

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Authors' Contributions

S.X. and T.J.W. were responsible for generation and collection of data, performed data analysis and interpretation, and drafted and approved the final version of the submitted manuscript. A.C.S., E.L.W., and J.L.V. were involved in conception and study design and revised and approved the final version of the manuscript. D.W.G. was responsible for generation/collection of data and revised and approved the final version of the manuscript.

Conflict of Interest

None declared.

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Professor Alice Smith has worked in kidney research since 1989. Over the last 15 years she has built up the Leicester Kidney Lifestyle Team (LKLT), a 20-strong multidisciplinary research team who aim to optimise the health and wellbeing of kidney patients through improved lifestyle management. Her bench-to-bedside translational research programme encompasses basic laboratory investigations of muscle metabolism and cardiovascular factors in CKD and the impact of lifestyle factors; clinical trials of the feasibility, efficacy and effectiveness of lifestyle interventions; evaluation of outcomes measures; qualitative research of patient and stakeholder perspectives; and the design, development, testing and implementation of behavioural interventions to encourage healthy lifestyle. All the research is underpinned by extensive and genuine patient and public involvement and engagement.

Abstract

Background: Assessment of cardiorespiratory fitness is an important outcome in chronic kidney disease (CKD). We aimed to develop a predictive equation to estimate peak oxygen uptake ($\text{VO}_{2\text{peak}}$) and power output (W_{Peak}), as measured during a cardiopulmonary exercise test (CPET), from the distance walked (DW) during the incremental shuttle walk test (ISWT).

Methods: Thirty-six non-dialysis CKD patients (17 male, age 61 ± 12 years, eGFR 25 ± 7 $\text{ml}\cdot\text{min}^{-1}\cdot 1.73\text{m}^{-2}$, BMI 31 ± 6 kg/m^2) carried out laboratory based CPET on a cycle ergometer and ISWT on two separate occasions.

Results: Linear regression revealed that DW/BMI was a significant predictor of $\text{VO}_{2\text{Peak}}$ ($r = 0.78$) ($\text{VO}_{2\text{Peak}}$ ($\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) = $[0.5688 \times (\text{DW}/\text{BMI}) (\text{m})] + 11.50$). No difference ($p = 0.66$) between CPET $\text{VO}_{2\text{Peak}}$ (19.9 ± 5.5 $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) and predicted $\text{VO}_{2\text{Peak}}$ (19.9 ± 4.3 $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) was observed. DW multiplied by body mass (BM) was a significant predictor of W_{Peak} ($r = 0.80$) (W_{Peak} (W) = $[0.0018 \times (\text{DW} \times \text{BM})] + 50.47$). No difference ($p = 0.97$) between CPET W_{Peak} 116.2 ± 38.9 W) and estimated W_{Peak} (113.9 ± 30.1 W) was seen.

Conclusions: The present study demonstrates that $\text{VO}_{2\text{Peak}}$ and W_{Peak} can be accurately estimated using the DW during an ISWT in CKD populations.

Introduction

Chronic kidney disease (CKD) is associated with reduced exercise capacity and increased cardiovascular disease risk (Go et al 2004). A growing body of research has shown that cardiorespiratory fitness, which can be reflected by peak oxygen consumption ($\text{VO}_{2\text{Peak}}$), is strongly related to a spectrum of health outcomes including cardiovascular disease and all-cause mortality (Blair et al 1996, Harber et al 2017). In the general population, low cardiorespiratory fitness is a greater indicator of mortality than any other traditional risk factor (Blair 2009, Shah et al 2016, Laukkanen et al 2004, Myers et al 2002). A study of young adults aged 18–30 over a period of 26 years reporting a significant relationship between high cardiorespiratory fitness and reduced risk of all-cause mortality (Shah et al 2016). Further, in men aged 42–60 years, with and without conventional risk factors for cardiovascular disease, $\text{VO}_{2\text{Peak}}$ represented a strong predictor of fatal and non-fatal cardiac events (Laukkanen et al 2004), and Myers et al (2002) showed, in a sample of 6213 men, each 1-MET increase in exercise capacity, equating to $3.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, conferred a 12% improvement in survival.

Unsurprisingly, given its multi-morbid nature, CKD patients have been markedly reduced cardiorespiratory fitness compared to age-predicted values (Howden et al 2015). Such poor levels of cardiorespiratory fitness are associated with greater cardiovascular burden (e.g., aortic stiffness, poor left ventricular function), and overall elevated risk of further morbidity and mortality (Howden et al 2015, Gulati et al 2012, Mackinnon et al 2018). Whilst no estimate exists in patients not requiring renal replacement therapy, in end stage renal disease $\text{VO}_{2\text{Peak}}$ values $>17.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ are a powerful predictor of survival (Sietsema et al 2004). Consequently, measuring cardiorespiratory fitness in CKD is fundamental for assessment of current and prognostic health status and survival.

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111 Cardiorespiratory fitness (measured as VO_{2Peak}) represents the ability to utilise oxygen during
112 increased metabolic demand (Bassett and Howley 2000). The ‘gold standard’ assessment of
113 VO_{2Peak} is through an incremental cardiopulmonary exercise test (CPET) (Palange et al 2007)
114 using breath-by breath sampling methods. However, these are poorly tolerated in older patients
115 with low fitness (Gill, DiPietro and Krumholz 2000), and require specialist costly equipment.
116 The incremental shuttle walk test (ISWT), a simple symptom-limited field test, has been used
117 as a surrogate marker of both VO_{2Peak} and peak power output (W_{Peak}) in clinical populations
118 such as chronic obstructive pulmonary disease (COPD) (Singh et al 1994, Arnardottir et al
119 2006). Both VO_{2Peak} and W_{Peak} can help set appropriate exercise intensities when prescribing
120 exercise, and our group have previously shown the ISWT and CPET to have good reliability
121 in CKD patients (Wilkinson et al 2018).

122

123 The aim of the present study was to develop prediction equations to estimate VO_{2Peak} and W_{Peak}
124 based on the distance walked (DW) during the ISWT. This can aid healthcare researchers and
125 professionals in the evaluation of patient health status, disease prognosis, and prescription of
126 appropriate exercise intensities for rehabilitation interventions without having to subject
127 patients to expensive and occasionally poorly tolerated laboratory testing.

Methods

Study design

This is a secondary analysis of baseline data collected during an exercise trial (#ISRCTN36489137) which took place between December 2013 and October 2016. A full description of the methods for this trial can be found in Watson et al (2018). The study was approved by the National Research Ethics Committee, East Midlands-Northampton (#13/EM/0344) and all participants gave informed consent.

Participants

Patients were recruited from nephrology outpatient clinics and included if they had CKD stages 3b – 5, and were not yet requiring dialysis. Exclusion criteria were: a) aged <18 years; b) body mass index (BMI) >40 kg/m²; c) physical impairment preventing undertaking of the study assessments; d) myocardial infarction within <6 months; e) any unstable chronic condition (e.g., diabetes); and f) inability to give informed consent.

Cardiopulmonary exercise testing

VO_{2Peak} was determined using a symptom limited, graded, maximal effort CPET performed on a cycle ergometer (Lode Excalibur, Groningen, The Netherlands). Participants underwent a full test familiarisation. Following a 3-minute warm-up at a resistance of 50 watts (W), patients were instructed to cycle >60 revolutions per minute (RPM). Work rate was increased using a ramp protocol of incremental workloads of 1W/ 4 seconds (15 W/ min) (Cortex Metasoft CPX software, Leipzig, Germany). The test was stopped if the RPM dropped <60 or if the participant reached volitional exhaustion. VO_{2Peak} and W_{Peak} (W) were calculated over a rolling 20-second average value.

Incremental shuttle walk test

The ISWT involved participants walking up and down a 10 metre (m) course (Singh et al 1994, Wilkinson et al 2018). Walking speed was controlled by an external auditory tone. The test was maximal and progressive, with an initial speed of 0.5 metres per second (m/s), increasing by 0.17 m/s every minute, for a maximum of 12 minutes. Standardised instructions were played before each test. The test was terminated when the participant felt they were unable to continue or if the participant was unable to sustain the speed for two continuous shuttles. The DW throughout the test was calculated. All participants completed a prior familiarisation test.

Statistical analysis

As a CPET provides relative oxygen uptake (e.g., $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$), we normalised ISWT results by systematically individually multiplying and then dividing the relative age, BMI, and body mass (BM) of the participants. These variables were selected as they are most likely to be available to healthcare professionals or researchers. Individual r values were calculated for each variable by assessing the relationship between each variable and $\text{VO}_{2\text{Peak}}$ and W_{Peak} (see **Table 1**). The variable with the highest r value was used to develop the prediction equations for $\text{VO}_{2\text{Peak}}$ and W_{Peak} .

Following selection of the most appropriate variable, linear regression was carried out: a) between the DW (m) divided by BMI (kg/m^2) and the $\text{VO}_{2\text{Peak}}$ ($\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) determined using CPET; and b) between the DW (m) multiplied by BM (kg) and the W_{Peak} (W) determined during the CPET. This elicited *adjusted* prediction equations for $\text{VO}_{2\text{Peak}}$ and W_{Peak} adjusting for BMI and BM respectively. To elicit *unadjusted* prediction equations for $\text{VO}_{2\text{Peak}}$ and W_{Peak} in conditions where BMI and BM measurements are absent, linear regression was also carried

out: a) between DW and the $\text{VO}_{2\text{Peak}}$ ($\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) determined using CPET; and b) between the DW (m) and the W_{Peak} (W) determined during the CPET.

Non-normally distributed data underwent log transformation. Paired sample t-tests were used to test for significant differences between values assessed using CPET and estimated $\text{VO}_{2\text{Peak}}$ and W_{Peak} using the prediction equation. Paired sample t-tests were also used to test for significant differences between estimated results using adjusted and unadjusted prediction equations ($\text{VO}_{2\text{Peak}}$: adjusted for BMI; W_{Peak} : adjusted for BM). Mean differences are shown along with 95% confidence intervals (95CI). Bland and Altman analysis plots assessed the agreement between values obtained during CPET and estimated using the prediction equations. Significance was set at <0.050 . Data analysis was performed using IBM SPSS Statistics 24 (IBM, USA).

Results

Out of the 54 patients consented to the main trial, 36 patients completed the CPET and the ISWT. Baseline characteristics for these patients are found in **Table 2**.

Adjusted prediction equations

Prediction of VO_{2Peak} using adjusted equations

Predicted VO_{2Peak} determined using the DW adjusting for BMI revealed the following equation ($r = 0.78$) (**Figure 1**):

$$\text{Predicted } VO_{2Peak} (ml.min^{-1}.kg^{-1}) = [0.5688 \times DW/BMI] + 11.504$$

The VO_{2Peak} measured during CPET of $19.9 (\pm 5.5) ml.min^{-1}.kg^{-1}$ was identical to that estimated using the prediction equation ($19.9 \pm 4.3 ml.min^{-1}.kg^{-1}$) (mean difference: 0.0 (95CI -1.2 to 1.2) $ml.min^{-1}.kg^{-1}$) ($p = 0.66$).

Prediction of W_{Peak} using adjusted equations

The DW during the ISWT multiplied by body mass was a significant contributor to the prediction of W_{Peak} ($r = 0.80$) eliciting the following equation (**Figure 1**):

$$\text{Predicted } W_{Peak} (W) = [0.0018 \times (DW \times BM)] + 50.47$$

Paired sample t-tests revealed no difference ($p = 0.96$) between W_{Peak} measured during CPET ($116.2 \pm 38.9 W$) and estimated W_{Peak} using the prediction equation ($113.9 \pm 30.0 W$) (mean

difference: 2.3 (95CI -5.7 to 10.3) W_{Peak}). **Figure 1** illustrates Bland and Altman plots with bias and limits of agreement at 95CI, plotted for each method for obtaining VO_{2Peak} and W_{Peak} using adjusted equations for either BMI or BM.

Unadjusted prediction equations

Prediction of VO_{2Peak} using unadjusted equations

Predicted VO_{2Peak} determined using the DW during the ISWT without adjusting for BMI revealed the following equation ($r = 0.74$) (**Figure 2**):

$$\text{Predicted } VO_{2Peak} (ml.min^{-1}.kg^{-1}) = [0.0216 \times DW] + 10.66$$

Paired sample t-tests revealed no significant ($p = 0.66$) difference observed between VO_{2Peak} measured by CPET ($19.9 \pm 5.5 \text{ ml.min}^{-1}.kg^{-1}$) and estimated VO_{2Peak} using the prediction equation ($19.9 \pm 4.0 \text{ ml.min}^{-1}.kg^{-1}$) (mean difference: 0.0 (95CI -1.2 to 1.3) $ml.min^{-1}.kg^{-1}$)

Prediction of W_{Peak} using unadjusted equations

Predicted W_{Peak} determined using the DW during the ISWT without adjusting for BW revealed the following equation ($r = 0.71$).

$$\text{Predicted } W_{Peak} (W) = [0.1465 \times DW (m)] + 54.639$$

Paired sample t-tests revealed no significant ($p = 0.55$) difference observed between W_{Peak} measured during CPET ($116.2 \pm 38.9 \text{ W}$) and estimated W_{Peak} using the prediction equation ($116.2 \pm 27.5 \text{ W}$) (mean difference: 0.0 (95CI -9.5 to 9.4) W_{Peak}). **Figure 2** illustrates Bland

241 and Altman plots with bias and limits of agreement at 95% CI, plotted for each method for
242 obtaining $\text{VO}_{2\text{Peak}}$ and W_{Peak} using unadjusted equations for either BMI or BM.

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Discussion

CPET is considered the ‘gold standard’ for measuring aerobic capacity, an important risk factor determining morbidity and mortality in CKD (Howden et al 2015, Gulati et al 2012). This is demonstrated by Gulati et al. (2012) who reported that $\text{VO}_{2\text{Peak}}$ values $<17.5 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ (~ 5 MET’s) combined with estimated glomerular filtration rate values of $<45 \text{ ml}\cdot\text{min}^{-1}\cdot 1.73\text{m}^2$ were associated with higher mortality rates compared to those with better aerobic capacity and eGFR. In the present study, we report an average of $\text{VO}_{2\text{Peak}}$ of $19.9 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ determined using CPET; these values are below that of comparative age-matched healthy sedentary individuals (Herdy and Uhlendorf 2011).

We found the relationship ($r = 0.78$) between DW during an ISWT and $\text{VO}_{2\text{Peak}}$ obtained during CPET support the findings of others in COPD ($r = 0.72$ (20), $r = 0.88$ (Singh et al 1994, Onorati et al 2003). Similar relationships ($r = 0.74$) have also been reported in idiopathic pulmonary fibrosis (Moloney et al 2003), and heart failure ($r = 0.83$) (Green et al 2001). It has been shown that $\text{VO}_{2\text{Peak}}$ determined using a treadmill based CPET is higher than $\text{VO}_{2\text{Peak}}$ values measured using a cycle based CPET (Myers et al 2009, Christensen et al 2004), thus a regression equation derived using a non-cycle walking based test could be expected to overestimate $\text{VO}_{2\text{Peak}}$ determined using an incremental cycle CPET. However, in the present study, average $\text{VO}_{2\text{Peak}}$ values determined during CPET ($19.9 \pm 5.5 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) were almost identical to estimated $\text{VO}_{2\text{Peak}}$ values determined using both formulas adjusted ($19.9 \pm 4.3 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) and unadjusted ($19.9 \pm 4.0 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) for BMI.

We also used the DW during the ISWT to develop a prediction equation of W_{Peak} . The relationship ($r = 0.80$) we observed between W_{Peak} obtained during CPET and estimated using

the prediction equation adjusted for BM supports research by Arnardottir et al (2006), who also showed a strong relationship ($r = 0.88$) between DW during the ISWT after controlling for body mass and W_{Peak} obtained during CPET in 93 COPD patients. Given the high prevalence of cardiovascular disease in CKD populations, many patients are prescribed β -blockers to manage hypertension. The confounding effects of this medication makes it difficult to prescribe exercise intensities according to heart rate target zones in this patient population. Therefore, the prediction equation in our study estimating W_{Peak} through DW during the ISWT may be more useful than the use of peak heart rate for the prescription of exercise in this patient population. Further, patients whom use a cycle ergometer in the gym or at home, and without knowledge of their heart rate, could set appropriate exercise intensities using W_{Peak} .

No significant differences were seen between data obtained using adjusted and unadjusted equations for VO_{2Peak} and W_{Peak} ($p = 0.93$; $p = 0.14$, respectively). This suggests that in the absence of BM or BMI measurements, the unadjusted equations still provide a valid means of estimating VO_{2Peak} and W_{Peak} . Being able to measure VO_{2Peak} and W_{Peak} using the ISWT does not make the ISWT a perfect substitute for the laboratory based incremental cycle test or other forms of laboratory based CPET. In the present study, slight variations were seen between estimated and measured peak values on an individual basis (as seen in the Bland and Altman plots with measures falling outside the 95%CI) however, when grouped, values showed no significant difference, making the ISWT together with our prediction equations a valid means of obtaining this data in the absence of expensive laboratory tests or when these tests are poorly tolerated by the patients.

Arnardottir et al (2006) discussed the possibility that the prediction equations they provided for COPD could be inversed, making it possible to calculate walking speed from W_{Peak}

determined during CPET. This is also possible with the equations presented in the present study. Given that the equations work both ways, it is possible to estimate the DW during an ISWT and therefore, walking speed from W_{Peak} determined during CPET. This may be useful in clinics that have laboratory based cycle testing as routine practice but want to prescribe walking based exercise instead of gym or home based exercise.

Study limitations

The patient population in the present study was an opportunistic sample obtained from a randomised clinical trial carried out by our group, and therefore the findings are limited by the characteristics of the cohort included. For example, the prediction equations may not be applicable to CKD patients outside the eGFR, BMI or age range studied. A larger and more diverse population would be required to tailor prediction equations for possible confounding factors such as BMI, gender, and ethnicity. Additionally, the present method of estimating VO_{2Peak} is only limited to people that can effectively carry out the walking test. Balance issues or visual impairments may influence the correct application of the walking test thus affecting predicted VO_{2Peak} values. Another possible limitation is our use of a cycle ergometer for the CPET, whereas a treadmill test may have provided a more relevant comparison to the ISWT. Indeed, previous studies have shown higher rates of O₂ consumption and CO₂ production in peak tests using a treadmill than a cycle protocol (Muscat et al 2015), although other exercise parameters did not differ between the two protocols. In this study, we chose to use the ergometer for patients safety reasons and because it is easier to standardise than a treadmill test and therefore likely provides more reproducible results, Furthermore, many patient participants are unfamiliar with exercise equipment and feel more confident to exert themselves seated on an ergometer than walking or running on a treadmill.

Implications for clinical practice

Cardiorespiratory fitness is a strong predictor of outcome and an important measure of health status in the general population and in chronic disease states, including CKD. CPET is the gold-standard method for measuring it but requires specialist equipment and a trained operator and is therefore costly and often inaccessible for general use by renal clinicians, nurses and other allied healthcare staff. In the present study, we have identified that the ISWT is a good predictor of cardiorespiratory fitness in non-dialysis CKD. We have developed adjusted and unadjusted formulae that use the DW during an ISWT and measures of BMI and BM to predict both VO_{2Peak} and W_{Peak} . This is of clinical importance as the ISWT is a considerably cost-effective and simpler method for estimating aerobic capacity. These formulae provide a simple means to estimate both VO_{2Peak} and W_{Peak} in non-dialysis CKD patients, which can be easily used as a field test by the renal multidisciplinary team.

Conclusions

The present study demonstrates that peak aerobic capacity and peak exercise capacity can be estimated using an ISWT with similar accuracy as CPET in non-dialysis CKD populations staged 3b–5. Early measures of cardiorespiratory and exercise capacity represent a quantifiable and prognostic biomarker of survival in this patient population. Therefore, the ability to evaluate and monitor improvements in peak aerobic capacity easily, coupled with the ability to set appropriate exercise intensities using W_{Peak} without the use of expensive equipment can provide a means to evaluate and improve the risk of adverse events.

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Table 1. Relationship between CPET values with adjusted and unadjusted ISWT values

	$\text{VO}_{2\text{Peak}} (r)$	$\text{W}_{\text{Peak}} (r)$
DW x Age	0.52	0.55
DW x BMI	0.57	0.72
DW x BM	0.64	0.80 [‡]
DW / Age	0.52	0.61
DW / BMI	0.78 [§]	0.59
DW / BM	0.73	0.48
DW	0.74	0.71

DW, distance walked during an incremental shuttle walk test; BMI, body mass index; BM, body mass; [§] variable used to create the prediction equation for estimating $\text{VO}_{2\text{Peak}}$; [‡] variable used to create the prediction equation for estimating W_{Peak}

411 **Table 2.** Patient characteristics

	<i>n</i> = 36
Age (years)	61 ± 12
eGFR (ml.min ⁻¹ .1.73m ²)	25 ± 7
Number of males	17
Ethnicity	
<i>White</i>	25
<i>Indian/ South Asian</i>	9
<i>Black Caribbean</i>	2
Body mass index (kg/m ²)	31 ± 6
Systolic/diastolic blood pressure (mmHg)	137 ± 13 / 80 ± 9
VO ₂ Peak (ml.min ⁻¹ .kg ⁻¹)	19.9 ± 5.5
ISWT distance walked (m)	430 ± 190
Haemoglobin (g/dL)	119 ± 15
Comorbid conditions	
<i>Diabetes, n (%)</i>	9 (25)
<i>Hypertension, n (%)</i>	15 (42)

412

413 Abbreviations: eGFR, estimated glomerular filtration rate; ISWT, incremental shuttle walk test

414

Figure 1.

(1A) the correlation between VO_{2Peak} measured during a cardiopulmonary exercise test (CPET) and the distance walked during an incremental shuttle walking test (ISWT) divided by body mass index (BMI);

(1B) a Bland and Altman scatterplot comparing VO_{2Peak} values obtained during CPET and estimated using the prediction equation;

(1C) the correlation between W_{Peak} (W) measured during CPET and the distance walked during the ISWT multiplied by body mass;

(1D) a Bland and Altman scatterplot comparing W_{Peak} values obtained during CPET and estimated using the prediction equation

Figure 2.

(2A) the correlation between VO_{2Peak} measured during a cardiopulmonary exercise test (CPET) and the distance walked during an incremental shuttle walking test (ISWT);

(2B) a Bland and Altman scatterplot comparing VO_{2Peak} values obtained during CPET and estimated using the prediction equation;

(2C) the correlation between W_{Peak} measured during CPET and the distance walked during an incremental shuttle walking test (ISWT);

(2D) a Bland and Altman scatterplot comparing W_{Peak} values obtained during CPET and estimated using the prediction equation